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06-1895-ag (CON), 06-2149-ag (CON), 06-2360-ag (CON)

In the U.S. Court of Appeals for the Second Circuit

Natural Resources Defense Council, Inc., Pesticide Action Network North America, Pineros y Campesinos Unidos Del Noroeste, Physicians for Social Responsibility-San Francisco, Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network,
Petitioners,
v.

United States Environmental Protection Agency,
Respondent.

On Petition for Review of an Order of the
United States Environmental Protection Agency

PETITIONERS' REPLY BRIEF

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INTRODUCTION

The challenged Human Testing Rule has harmed and will continue to harm Petitioners and their members. The substantial and entirely uncontroverted evidence before this Court belies EPA's factual assertions to the contrary, and this Circuit and the Supreme Court have both rejected EPA's core Article III legal theory. The Court has jurisdiction and should proceed to the merits.

EPA's Human Testing Rule violates Section 201 because it allows intentional pesticide toxicity experiments on pregnant women and children in some circumstances, contravenes the principles proposed by the National Academy's 2004 Report, and is inconsistent with the Nuremberg Code. EPA ignores the statute's clear text in favor of an allegedly narrow legislative "policy," but disregards the stated policy of Section 201's enactors. EPA argues that most of the Nuremberg Code is precatory, although text and history show otherwise. EPA treats the National Academy's proposals as distractions, and disregards the evidence and canons of construction that disprove that treatment.

In short, EPA asks this Court to rewrite the law. The invitation should be rejected.

ARGUMENT

I. Petitioners Have Standing

The Human Testing Rule has caused EPA to raise exposure limits for pesticides to which Petitioners' members are exposed. A judicial order vacating the Rule would remove the cause of this injury. Petitioners' uncontroverted evidence establishes these facts and each element of Article III standing.

A. The Human Testing Rule Injures Petitioners and Their Members

Exposure to a toxic chemical is a well-recognized Article III injury. *See, e.g., Friends of the Earth, Inc. v. Laidlaw*, 528 U.S. 167, 184-85 (2000); *LaFleur v. Whitman*, 300 F.3d 256, 270 (2d Cir. 2002). Indeed, this Court has held that even "health-related uncertainty," *see New York Public Interest Research Group v. Whitman*, 321 F.3d 316, 325, 326 (2d Cir. 2003) ("*NYPIRG*"), or an "increased risk" of exposure to a dangerous substance, *Baur v. Veneman*, 352 F.3d 625, 633 (2d Cir. 2003); *see also id.* at 627-28, 633-35, 641-42, are constitutionally cognizable.[1]

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[1] This Court's recognition that increased risk of harm is a cognizable injury comports both with common experience (e.g., people pay for insurance against risks of future injury) and with the law of other Circuits. *See Central Delta Water Agency v. United States*, 306 F.3d 938, 947-948 (9th Cir. 2002); *Hall v. Norton*, 266 F.3d 969, 976 (9th Cir. 2001); *Johnson v. Allsteel, Inc.*, 259 F.3d 885, 888 (7th Cir. 2001); *Friends of the Earth, Inc. v. Gaston Copper Recycling Corp.*, 204 F.3d 149, 160 (4th Cir. 2000); *Louisiana Envtl. Action Network v. EPA*, 172 F.3d 65, 67-68 (D.C. Cir. 1999); *Walters v. Edgar*, 163 F.3d 430, 434 (7th Cir. 1998), *cert.*

The uncontroverted evidence proves precisely such injuries here. Petitioners' members include farmworkers who apply and are exposed to pesticides in the fields where they work; families who live downwind of agricultural spray; and consumers who eat and drink pesticide-contaminated food and water in their normal diet. *See* D8-9, D84-88, D89-90, D91, D92, D93, D94, D96-97, D98, D106-08, D112-14, D117, D122-24, D350.[2] These individuals have "no choice but to breathe the air where [they] live[] and work[]" or to eat the food on their table. *LaFleur*, 300 F.3d at 270; D8-D9, D11-12; D101-102.

The pesticides at issue can cause severe neurological, developmental, and other disorders. *See* D6, D9, D12, D15-16, D28, D101-04. When EPA raises allowable exposure limits for these chemicals, people who live, work, and eat downwind or downstream will thus "undoubtedly" experience "increased levels" of exposure, practically "whenever the wind blows . . . in [their] direction." *LaFleur*, 300 F.3d at 270. Such increased exposure exacerbates health risks and

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denied, 526 U.S. 1146 (1999); *Mountain States Legal Found. v. Glickman*, 92 F.3d 1228, 1234-35 (D.C. Cir. 1996).

[2] Petitioners have concurrently filed a volume of Declarations in Support of Standing, citations to which in this brief follow the form "D[page number]." This volume includes evidence submitted with Petitioners' August 3, 2006 Response to EPA's Motion to Dismiss, including the expert declarations of Gina Solomon, M.D., Adam M. Finkel, Sc.D., Margaret Reeves, Ph.D., and Karen Mountain, M.B.A., M.S.N., R.N., as well as additional percipient witness declarations of Petitioners' members and officers. The declarations volume also includes additional expert and percipient witness declarations that relate to subsequent EPA actions, as well as to a standing issue that EPA did not raise until its merits brief and which is addressed *infra*, at Section I.C.

uncertainty.[3] *See* D5-6, D9, D11-12, D15-16, D28-29, D30, D41, D57, D63-64, D84-88, D90, D91, D92, D107-08.

The Human Testing Rule[4] caused EPA to set higher pesticide exposure limits for the pesticides at issue. Promulgation of the Rule lifted Section 201's moratorium on EPA use of human toxicity experiments to set pesticide standards and, shortly after the Rule took effect, EPA began relying on such experiments to increase allowable exposure limits for these pesticides. For example, EPA increased allowable exposure levels for aldicarb, amitraz, dichlorvos, and methomyl – neurotoxins all – by as much as three, five, and even ten times the levels EPA would have set but for its use of these human studies. *See* D9-11, D12, D15, D18-19, D28-29, D31, D54-55, D162-166, D219, D225, D230-231, D381; *cf. Baur*, 352 F.3d at 637 n.11 (holding that evidence of post-filing events can "confirm that a plaintiff's fear of future harm is reasonable").

EPA's reliance on the Human Testing Rule to increase allowable pesticide exposure levels was not only a possible, but the predictable result of the Rule. When the Rule issued, EPA faced an imminent August 2006 deadline for

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[3] The precise level of risk posed by increased exposure is not itself a question of Article III significance. *See Baur*, 352 F.3d at 642-43; *cf. Havens Realty Corp. v. Coleman*, 455 U.S. 363, 379 (1982) (holding that even a "perceptibl[e]" injury satisfied Article III).

[4] EPA used to refer to the subject of its rule as "Human Testing," *e.g.*, 70 Fed. Reg. 6661 (Feb. 8, 2005), and to call it the "Human Studies Rule," A1274. That name is more precise than EPA's new term, "Research Rule."

reregistering numerous pesticides and reassessing thousands of pesticide tolerances (i.e., deciding which pesticides and which food uses were sufficiently safe to continue). *See* 21 U.S.C. § 346a(q); 7 U.S.C. § 136a-1(g)(2)(A)(i). To meet that August deadline, EPA relied on human experiments that had already been conducted, and the results of which (purporting to justify a relaxation in pesticide protections) were thus known. *See, e.g.*, A156, A666, A704-06; D130; Wall Decl. in Supp. of Mot. to Complete Admin. R. (Sept. 28, 2006), Ex. B at 2 (EPA memo from July 2005 reciting how EPA could use dichlorvos human study to justify tenfold increase in exposure levels).

Moreover, EPA's promulgation of the Rule resulted in two critical changes to the way EPA set these pesticides standards. First, as noted above, the Rule lifted Section 201's moratorium on EPA use of human toxicity experiments. SPA1. Second, EPA's use of the experiments changed EPA's calculation of allowable exposure levels for a number of pesticides. Under EPA's standard risk assessment methodology, whenever EPA relies on only animal experiments to assess risk, it applies a tenfold safety factor to account for the prospect that humans are more susceptible than animals. A153; D3-5, D44-46, D49-51. Where EPA uses human experiments, it reduces or eliminates this safety factor. Thus, EPA's use of human studies predictably caused EPA to reduce or waive the tenfold safety factor and calculate significantly higher allowable exposure levels for these

pesticides. D3, D5, D28-29, D49-55. This expected result was, of course, precisely why the pesticide manufacturers began aggressively submitting human toxicity tests to EPA in the first place. *See* Pet'rs. Br. 13-14; A666.[5]

In light of this evidence, EPA's description of Petitioners' injury as "speculative" – or, with some rhetorical gusto, as "a hypothetical injury associated with the possibility of higher exposure levels that might be established in future EPA proceedings" – is perplexing. EPA Br. 1-2. The events that EPA calls "speculative" have in fact already occurred. EPA itself admits this, noting that "[t]he declarations and documents submitted by Petitioners related to recent EPA actions regarding tolerance levels demonstrate that this multi-step path was followed in the post-Research Rule actions cited by Petitioners." EPA Br. 25.

The harm to Petitioners' members here is thus far more certain than other, future harms this Court has found to satisfy Article III in previous cases, including a risk that EPA's approval of a flawed state permitting program might cause later increases in air pollution, *see NYPIRG*, 321 F.3d at 324, 325-26, and the risk from a regulation that increased the prospect of exposure to mad cow disease, a pathogen that had not yet been discovered in this country, *see Baur*, 352 F.3d at

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[5] Because EPA's Human Testing Rule fails to adopt basic scientific safeguards recommended by the National Academy of Sciences, many of the human toxicity experiments considered by EPA lack the statistical power to detect adverse health effects that would be experienced across a wider population. A60-62; D6-7, D48, D59-61. When EPA relies on such studies, the result is an increase in risk to those exposed. *See id.*; *see also* D11, D15, D19, D29, D41, D63-64.

633-355, 642. EPA ignores this evidence and precedent, instead arguing that an injury is *always* too speculative – as a matter of law – if the challenged agency action is not the very last step in the causal chain. EPA Br. 21, 23, 27 & n.5. As we discuss in the next section, that theory has been rejected both by the Supreme Court and by this Circuit.[6]

B. Petitioners' Injuries Are Fairly Traceable to EPA's Rule

Uncontroverted evidence establishes that the Human Testing Rule changed EPA's pesticide standard setting process, causing EPA to waive a tenfold uncertainty factor and thus, predictably, to increase allowable exposure levels for pesticide to which Petitioners members are exposed. *See supra*, at Section I.A. EPA contends that despite this evidence, Petitioners cannot satisfy Article III's

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[6] Petitioners have standing to sue to protect their own organizational interests, as well as those of their members. Petitioners Pineros y Campesinos Unidos del Noroeste and Farm Labor Organizing Committee, AFL-CIO, for example, expend resources to investigate and respond to pesticide incidents affecting any of their numerous members. *See* D111, D113-16; D124-26. Petitioner Migrant Clinicians Network expends resources training the thousands of doctors, nurses, and other clinicians it represents to respond to such incidents. *See* D117-20. The resulting costs to Petitioners are established Article III injuries, *see Havens*, 455 U.S. at 379; *cf. Sierra Club v. Morton*, 405 U.S. 727, 737-38 (1972), that are "germane," *Hunt v. Washington State Apple Advert. Comm'n*, 432 U.S. 333, 343 (1977), to Petitioners' purposes. *See* D93, D99-100, D109, D117, D12. Indeed, the chance that one of Petitioners will expend resources to respond to such an incident is the aggregate of the risk to all of their thousands of members. *See* D109, D116, D117-19, D122; *cf. Utility Air Regulation Group v. EPA*, __ F.3d __, No. 05-1353, 2006 WL 3590194, *6 (D.C. Cir. Dec. 12, 2006) ("[G]iven the organization's large membership . . . we find it reasonable to infer that at least one member will suffer injury-in-fact.").

causation requirement because EPA's Rule was not the very last, or "operative," cause of their injury. EPA Br. 26-27 & n.5. Precedent says otherwise.

The Supreme Court expressly rejected EPA's argument a decade ago, in *Bennett v. Spear*, 520 U.S. 154 (1997). The *Bennett* plaintiffs sued the Fish and Wildlife Service ("FWS") over a biological opinion FWS provided to the Bureau of Reclamation ("Bureau"). *Id.* at 159. FWS challenged plaintiffs' standing, claiming that its biological opinion was not the "proximate cause" of the plaintiffs' anticipated injuries, which would occur (if at all) only after an "as yet unidentified" later decision by the Bureau. *Id.* at 168. The Court, per Justice Scalia, rejected that theory as "wrongly equat[ing] injury 'fairly traceable' to the defendant with injury as to which the defendant's actions are the very last step in the chain of causation."[7] *Id.* at 168-69; *see also Metropolitan Washington Airports Auth. v. Citizens for Abatement of Aircraft Noise*, 501 U.S. 252, 261-62, 264-65 (1991) (holding plaintiffs had standing to challenge a law that gave a review board power

[7] *Bennett* found the plaintiffs' injury "fairly traceable" to the FWS biological opinion because the facts supported that finding. The Court concluded that the FWS biological opinion would be "virtually determinative" of the Bureau's later decision because, if the Bureau disagreed with FWS, it would have to articulate the basis for its disagreement on the record and run the risk of being sued if it were wrong. 520 U.S. at 169, 170. Far from distinguishing the present case, this aspect of *Bennett* supports Petitioners' standing here. Petitioners' uncontroverted causation evidence – including the extensive testimony of one of the leading risk assessment experts in the country, *see* D37-41 – is both stronger and more direct than the circumstantial evidence *Bennett* found sufficient. Moreover, *Bennett* approached causation with particular care because the ultimate agency actor in that case, the Bureau, was not even a party. *Id* at 169. The same is not true here.

to veto a development plan because the power, although unexercised, had "influenced" plan adoption).

This Circuit, too, has rejected EPA's "operative cause" theory of standing. In *NYPIRG*, for example, the petitioners challenged EPA's authorization of New York's air pollution permit program.[8] 321 F.3d at 320-22, 324. EPA's approval of that program did not itself require or permit any increase in air pollution. Such a pollution increase would arise, if at all, only when New York later issued permits under its flawed program. This Court nevertheless found standing because EPA's authorization of the state program would increase the petitioners' members' "uncertainty" about pollution from nearby factories. *Id.* at 325-26. EPA's decision to permit the New York program was not the final step in the causal chain; EPA was not even the final actor. Yet standing existed because the members' injuries were "fairly traceable" to EPA's decision. Under *NYPIRG*, Petitioners here plainly have standing.

The two out-of-Circuit decisions on which EPA relies do not support a departure from this Court's precedent. In *Louisiana Environmental Action Network v. Browner*, 87 F.3d 1379 (D.C. Cir. 1996) ("*LEAN*"), the plaintiffs challenged an EPA rule that they feared would create an "enforcement gap," but

[8] EPA mischaracterizes *NYPIRG* as a challenge to an EPA decision that "regulated emissions of air pollutants from several facilities." EPA Br. 22. *NYPIRG* involved, and found standing for, three consolidated lawsuits, at least two of which EPA's characterization ignores. 321 F.3d at 324.

apparently presented no evidence that such an enforcement gap was likely, let alone likely where their members lived. *Id.* at 1383. At most, *LEAN* shows that an injury based on future agency action *can* be too speculative where the plaintiff introduces no evidence to prove causation; it does not show that such an injury is *always* too speculative, regardless of the evidence. As for *Shoreham-Wading River Central School District v. Nuclear Regulatory Commission*, 931 F.2d 102, 105 (D.C. Cir. 1991), its holding – that a plaintiff lacks standing to challenge an agency action if that action is a "but for" cause of the plaintiff's injury but not the "operative" cause – did not survive *Bennett*, 520 U.S. at 168-69, and has never been cited by any published decision of any court.

C. Petitioners Have Standing to Challenge the EPA's Failure to Regulate All Toxicity Experiments Covered by Section 201

Petitioners' uncontroverted evidence also establishes standing to challenge the Rule's failure to regulate human dosing pesticide toxicity experiments (including experiments on pregnant women and children) unless "intended" for EPA's consideration under FIFRA or FFDCA. EPA uses human toxicity experiments to set pesticide standards under other statutory programs, *see* Pet'rs. Br. 9-10, D29-33, as do other governmental agencies, *see, e.g.*, Pet'rs. Br. 28 & n.9; D33-34. Regulatory decisions under these other statutes increase Petitioners' members' risks of exposure in precisely the same way as do EPA's decisions under FIFRA and FFDCA.

For example, EPA regulates human exposure to pesticides under the Safe Drinking Water Act ("SDWA"), 42 U.S.C. § 300g-1(b). *See, e.g.,* 40 C.F.R. § 141.61(c) (setting SDWA maximum contaminant levels for numerous pesticides). Tens of thousands of Petitioners' members live in cities for which the source of drinking water has been contaminated with pesticides, including aldicarb, methomyl, and oxamyl – all chemicals for which EPA has received and is considering human dosing toxicity experiments. *See* D30-31, D91, D92, D95, D96-97, D98, D233 (¶ 4), D350. EPA is required by SDWA to reevaluate all existing drinking water standards every six years,[9] *see* 42 U.S.C. § 300g-1(b)(9), and to set new standards periodically, *see id.* at § 330g-1(b)(1)(B)(ii). It is predictable that when EPA does so, reliance on human experiments will lead to increases in allowable exposures levels, as has been true in EPA's FIFRA and FFDCA risk assessment process. 40 C.F.R. § 141.61(c); D28-29, D32-33.

Indeed, pesticide-industry human toxicity studies have already caused EPA to reduce drinking water protections for at least one pesticide. EPA set a drinking water standard for aldicarb, but later suspended that standard when the pesticide's manufacturer claimed that EPA had improperly relied on an animal study and should instead have relied on a particular human study. 57 Fed. Reg. 22178, 22179 (May 27, 1992). EPA reconsideration of that aldicarb drinking water

[9] EPA last reevaluated its oxamyl drinking water standard, for example, in 2003. *See* 68 Fed. Reg. 42908 (July 18, 2003).

standard is still pending, and EPA is considering human studies in that ongoing proceeding. *See id.* Had EPA's Human Testing Rule complied with Section 201, however, a different and more protective standard would govern EPA's use of human studies in that and other drinking water standard setting proceedings.[10]

Petitioners cannot wait to challenge EPA's failure to regulate the conduct and use of such experiments – which are covered by Section 201 but ignored by EPA's Rule, *see* Section II, *infra* – in assurance that a challenge could be launched when EPA uses such an experiment in a later proceeding. Were Petitioners to delay in challenging the unlawfully narrow scope of the Rule, EPA would no doubt argue that the FFDCA's sixty-day statute of limitations barred their litigation. *See* 21 U.S.C. § 346a(h)(1); *cf. NRDC v. Johnson*, 461 F.3d 164, 173-176 (2d Cir. 2006) (reading this FFDCA provision's judicial review exclusivity clause broadly).

Petitioners have challenged EPA's Rule in part to protect their members from predictable future risks resulting from the Rule's unlawfully narrow scope. As was the case in *NYPIRG*, 321 F.3d at 325-26, and *Baur*, 352 F.3d at 633-35, Article III poses no obstacle to this suit.

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[10] EPA's own aldicarb risk assessment shows that, when drinking water exposures are included, risks to every subgroup considered – the general population, infants, children age 1-2, and females age 13-49 – exceed the risk thresholds EPA would have used had it relied on an animal study rather than a human experiment. D29, D277 (defining level of concern), D279 (comparing exposure to human-based and animal-based levels of concern).

II. The Rule Violates Section 201's Blanket Ban on the Use of Pregnant Women and Children as Subjects in Pesticide Toxicity Experiments

Section 201 directed EPA to issue a rule, applicable to "intentional dosing human toxicity studies for pesticides," that "shall not permit the use of pregnant women, infants, or children as subjects." SPA1. There is no dispute that EPA did not adopt such a categorical rule. Instead, the Human Testing Rule regulates only those toxicity experiments that are "intended" to be submitted to EPA for consideration under FIFRA or FFDCA. SPA40 (§ 26.1201). The Rule's narrow scope violates Section 201 by, among other things, permitting many pesticide toxicity experiments on pregnant women and children and allowing EPA to consider such tests under statutes other than FIFRA and the FFDCA. These other statutes include the Safe Drinking Water Act and Clean Water Act, pursuant to which EPA also regulates human exposure to pesticides. *See* Pet'rs. Br. 9-10.[11]

EPA's contention that its narrowing construction conforms to Section 201's "object and policy," EPA Br. 30, fails for two reasons. First, the task of interpreting statutory language properly begins, not with an inquiry into "purpose," but with the statutory language itself. *See, e.g. Raila v. United States*, 355 F.3d 118, 120 (2d Cir. 2004) ("Statutory construction begins with the plain text, and, 'where the statutory language provides a clear answer, it ends there as well.'"

[11] Pesticides contaminate drinking water and surface waters regulated by the Safe Drinking Water Act and Clean Water Act when the pesticides run off agricultural fields or facilities where they have been applied.

(internal citation omitted)). "[A]lthough a court appropriately may refer to a statute's legislative history to resolve statutory ambiguity, there is no need to do so here," because the statutory text itself is clear. *Toibb v. Radloff*, 501 U.S. 157, 162 (1991). "Studies for pesticides" means just that – *i.e.,* "studies with respect to pesticides," *see* Random House Unabridged Dictionary 747 (2d ed. 1993) (defining "for") – not "studies for pesticides intended for EPA's consideration under FIFRA or FFDCA." Where, as here, "the statutory language is unambiguous and 'the statutory scheme is coherent and consistent,'" judicial inquiry "must cease." *Robinson v. Shell Oil Co.*, 519 U.S. 337, 340 (1997) (internal citation omitted).

EPA originally acknowledged Section 201's obvious meaning. Shortly after Section 201's enactment, EPA issued a formal interpretative Guidance that concluded that the phase "studies for pesticides" encompassed studies *of* pesticides, even if not "submitted or otherwise available for consideration under [FIFRA or FFDCA § 408]." Wall Decl. in Supp. of Mot. to Complete Admin. R. (Sept. 28, 2006), Ex. A-1 at 14-15 (EPA Guidance setting out "[w]hat is meant by a study 'for pesticides'"). EPA's original administrative usage "confirms our understanding of the everyday sense of the term." *S.D. Warren Co. v. Maine Bd. Envt'l Prot.*, 126 S. Ct. 1843, 1849 (2006).[12]

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[12] EPA's brief attempts to minimize the force of the Agency's original interpretation by labeling the Guidance "interim" and asserting it was drafted "broadly" to "avoid inadvertent noncompliance" with Section 201. EPA Br. 36.

Second, even if the statutory text were not clear, the legislative history belies EPA's claim that Congress intended to prohibit only those studies conducted and submitted for FIFRA and FFDCA purposes. EPA identifies no statement, from any Member of Congress, that Section 201 would allow dosing pregnant women and children with pesticides if the experiment was intended for EPA's use under other laws. When Senator Burns proposed an amendment that would have applied Section 201 to existing studies only if "submitted to the Agency under FIFRA," 151 Cong. Rec. S7552 (June 29, 2005), the Conferees rejected that approach, SPA1. *See* Pet'rs. Br. 21, 30.[13]

Instead, the legislative history shows that Section 201's proponents were appalled that researchers were dosing pregnant women and children with pesticides *at all*. Representative Solis, the lead House sponsor, summarized this sentiment, saying: "[i]t should never have taken place, the testing of pesticides on humans, particularly children." A647. Senator Boxer, the lead Senate sponsor, asked "what more of a moral issue can we be facing than allowing these students to have

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This explanation, which rests entirely on litigation counsel's say so rather than citation to the record, does not advance EPA's cause; the Agency obviously remains obliged to "avoid . . . noncompliance" with Section 201, inadvertent or otherwise.

[13] Nothing in the record remotely supports EPA's new assertion that Section 201 will deter development of mosquito repelling products. EPA Br. 34 n.10. Pesticides need not be applied to *children* to test their effectiveness against *mosquitoes*, and EPA has repeatedly made clear it does not need human studies to regulate pesticides in a manner that is protective of human health. *See* 151 Cong. Rec. H3671; A650.

chloropicrin pumped through their nostrils at a level 12 times higher than the safety level that OSHA, our Federal Government, says is safe?" 151 Cong. Rec. S7553 (June 29, 2005). Criticizing another study, involving infants, Section 201's co-sponsor, Senator Nelson, wondered: "Can anyone believe this is going on in the United States of America in the year 2005? . . . I certainly was not going to let that sort of thing go on in my State and it should not be going on in any State." 151 Cong. Rec. S7553-S7554 (June 29, 2005).

These floor statements reflect congressional recognition that the dangers of human dosing experiments have nothing to do with whether the study is intended for EPA's consideration under a particular statute. The dangers inhere in the experiments. This is why Section 201 expressly applies not only to EPA's "consider[ation]" of such experiments, but also to the studies' "conduct," regardless of the study sponsors' intentions.[14] SPA1.

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[14] Some of the studies that horrified Section 201's proponents were no doubt intended for EPA consideration under the FQPA. This hardly proves EPA's claim, EPA Br. 31-33, that despite the clear language of Section 201, Congress meant *not* to regulate identical experiments conducted with a different intention. Indeed, a number of the studies that Section 201's sponsors condemned were conducted long before the FQPA was enacted. A705-06. EPA cites no evidence that these studies were "intended" for use under FIFRA or FFDCA.

III. The Rule Contravenes the National Academy's Proposed Principles

Section 201 required EPA to promulgate a rule that "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing." SPA1. The Academy's Report makes only one set of proposals; they are set forth in seventeen, enumerated Recommendations. Petitioners' opening brief demonstrated that EPA's Rule is inconsistent with these Recommendations, and EPA does not disagree.

Instead, EPA claims that when Congress referred to the "principles proposed by the 2004 report of the National Academy of Sciences," Congress was referring to three principles ("beneficence," "justice," and "respect for persons") identified in a 1979 document called the "Belmont Report." A1286. EPA contends that these three "principles" are also "contained in the NAS Report," EPA Br. 37, and "form the basis for *many* of" the Report's recommendations, EPA Br. 39 (emphasis added). From these premises, EPA urges the Court to conclude that the Belmont Report's principles are "the principles proposed" by the Academy, and adopted by Congress, even though neither the text of Section 201 nor its legislative history ever mention these principles.

A threshold difficulty with EPA's argument is that Congress did not require consistency with some subset of principles "contained in" (EPA Br. 37) the Academy's Report. Congress required consistency with the principles that Report

"proposed." SPA1. A "proposal" is, of course, a "recommendation." *Random House Unabridged Dictionary* 1551 (2d ed. 1993). The Academy explicitly set forth its "proposals" in its Recommendations. A129 ("Because of . . . the need to be specific about the proposals being made, the recommendations follow.").

By contrast, the Academy never "proposed" the Belmont principles, let alone proposed those principles as *the* sole principles of the Academy's Report. The Belmont Report was just one of the several "authoritative statements" that the Academy concluded *collectively* represented the (then-existing) "basic standards that govern human research in the United States." A127, 234; Pet'rs. Br. 46-47. Far from "proposing" these principles, however, the Academy found them too "unclear, indeterminate, inconsistent, and frequently contradictory" to provide appropriate guidance for toxicant research. A235. This was why the Academy offered its "own judgments," *id.*, as set forth in its Recommendations. EPA's selective adoption of the most "unclear" and "indeterminate" of the several pre-existing statements of principle would turn the Academy's work on its head.[15]

EPA's claim (EPA Br. 37) that the Academy's Recommendations do not set forth "principles" is also wrong. In one meaning, a "principle" is "a standard . . .

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[15] EPA's unprincipled selectivity is highlighted by its implicit admission that the Belmont principles were not a basis for all of the Academy's proposals. EPA Br. 39. For example, the Belmont principles were never mentioned in the Academy's chapter setting forth scientific principles, which is not surprising, since the Belmont Report addresses ethics, not science. A189-206.

for guiding conduct or practice," *Random House Unabridged Dictionary* 1539 (2d ed. 1993). This meaning aptly describes the Academy's Recommendations. That this was the meaning Congress used in Section 201 is demonstrated by Section 201's other use of this word to refer to the "principles of the Nuremberg Code." EPA concedes that the Nuremberg Code's "principles" are the ten standards enumerated in that Code. A529. Notably, the Nuremberg Code's principles are specific, codified rules of conduct. They are similar in enumeration, structure, and detail to the Academy's Recommendations – and entirely dissimilar to the Belmont Report's vague invocations of "justice," "beneficence," and "respect." Thus, Congress' use of the phrase "principles proposed" to refer to the Academy's Recommendations is not only consistent with common usage, it is the only usage of "principles" that is consistent with Congress' other use of that same word, in the same sentence, to refer to the Nuremberg Code.

Nor does our reading of the statute render Section 201's requirement of an "*independent* Human Subjects Review Board," SPA1 (emphasis added), redundant with the Academy's recommendation of a "Human Studies Review Board," A258. The Academy proposed a Review Board "internal" to EPA and explicitly recommended that this Board *not* be "independent." A259. Congress' requirement of an "independent" board is thus not "redundant," EPA Br. 38, but reflective of Congress' disagreement with this single aspect of the Academy's proposals.

To be sure, Congress *could* have referred to the Academy's seventeen proposals as "Recommendations," rather than as "principles proposed," but there was no need for Congress to do so. The English language is sufficiently resilient to allow Congress to choose among words and phrases that, in context, convey the same meaning. In ordinary English, "principles proposed" means "recommended standards for guiding conduct." That phrase succinctly and accurately describes the Academy's Recommendations.

Congress' meaning is confirmed by the legislative history. The floor debates are replete with statements by Section 201's proponents that the law would require EPA to abide by the Academy's "recommendations." 151 Cong. Rec. H7019; 151 Cong. Rec. H7020-H7021; Pet'rs. Br. 44-45. The Belmont principles are not mentioned. This legislative history thus reinforces the textual analysis.

"Even for an agency able to claim all the authority possible under *Chevron*, deference to its statutory interpretation is called for only when the devices of judicial construction have been tried and found to yield no clear sense of congressional intent." *General Dynamics Land Sys., Inc. v. Cline*, 540 U.S. 581, 600 (2004). Here, the text and history of Section 201 do provide a "clear sense" that Congress intended EPA to conform to the Academy's Recommendations, not the Belmont principles. EPA's unreasonable interpretation should be rejected.

IV. The Rule Violates the Nuremberg Code and FIFRA Section 12

Section 201 requires EPA's Rule to be "consistent" with the Nuremberg Code. SPA1. In normal usage, "consistent" means "agreeing or accordant." *See Random House Unabridged Dictionary* 434 (2d ed. 1993). The Human Testing Rule, however, authorizes human experiments that are not consistent with, and in some cases violate, the Nuremberg Code. The Rule also contravenes FIFRA section 12(a)(2)(P). SPA2.

A. The Rule Authorizes Toxicity Experiments Without the Subject's Fully Informed, Comprehending, and Voluntary Consent

Petitioners' opening brief showed that EPA's Rule allows someone other than the human subject to "consent" to the experiment, in violation of the Nuremberg Code and FIFRA section 12(a)(2)(P); fails to require that the human subject be free of "any element . . . of constraint or coercion," in violation of the Nuremberg Code; and fails to ensure that the human subject "comprehen[ds]" the risks, also in violation of the Nuremberg Code. *See* Pet'rs. Br. 49-55; A529. EPA's defenses are unpersuasive.

EPA first suggests that all the studies with which Petitioners are concerned – studies that EPA admits contained "misleading statements in the informed consent materials" – are irrelevant because those studies "took place *prior*" to the Rule. EPA Br. 45 (emphasis in original). EPA misses the point. Section 201 does not only restrict EPA's consideration of experiments that may be conducted in the

future. It also restricts EPA's consideration of *existing* studies, including studies conducted before the Rule was promulgated. Section 201's text suggests no exception for EPA consideration of past studies, SPA1, and the legislative history makes clear Congress' specific purpose to stop EPA from using these studies. A647 (Rep. Solis) ("All of the studies currently pending before EPA . . . fall far short of the stringent criteria for EPA consideration outlined by the NAS and the Nuremberg Code, and required by this amendment."); 151 Cong. Rec. S7553 (June 29, 2005) (Sen. Boxer) (similar); 151 Cong. Rec. S7557 (June 29, 2005) (Sen. Burns) (critiquing Boxer amendment for prohibiting use of existing studies).

Nor does the Rule ensure prospective consistency with the Nuremberg Code. The Agency's lead argument is that because the Nuremberg Code's first principle uses the word "should," rather than "shall," most of the principle is optional. EPA Br. 46. Consistency with an optional principle would not be difficult. However, EPA's argument ignores the first sentence of this principle: "The voluntary consent *of the human subject* is absolutely essential." A529 (emphasis added). Consent by someone other than the human subject violates this standard.

EPA's argument would also eviscerate virtually the entire Nuremberg Code, as well as Congress' direction to conform to that Code. "Should" is the operative word in nine of the Nuremberg Code's ten principles – none of which use "shall." A529. That the Nuremberg Code uses the language of ethics ("should"), rather

than the mandatory language of law ("shall"), cannot mean that Congress intended compliance with its principles to be voluntary. If that were the case, the most fundamental requirements of the Code – including the principles that a human subject "should" be protected against death or disability (Principle 7) and "should" be able to withdraw from an experiment while it is underway (Principle 9) – would amount to little more than a nice idea.[16]

Petitioners do not, as EPA claims (EPA Br. 44), demand "exact correspondence" between EPA's Rule and the text of the Nuremberg Code. What Section 201 requires is substantive consistency. EPA's Rule allows experiments to be conducted that violate the Code. The Rule is therefore inconsistent with that Code and Section 201.[17]

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[16] EPA's "should" argument also fails because EPA did not articulate this rationale at any point during the Rulemaking. *See Motor Vehicle Mfrs. Ass'n, Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 50 (1983) (agency action "must be upheld, if at all, on the basis articulated by the agency itself"); *Gifford Pinchot Task Force v. U.S. Fish & Wildlife Serv.*, 378 F.3d 1059, 1072 n.9, 1074 (9th Cir.) (a court may "only rely on what the agency said in the record"), *amend. on other grounds*, 387 F.3d 968 (9th Cir. 2004).

[17] EPA's defenses to two of Petitioners' other concerns are equally unavailing. First, the Rule's direction only to "minimize the possibility of coercion or undue influence" plainly does not ensure that a human subject must "be able to exercise free power of choice, *without* . . . *any* element of . . . constraint or coercion," as required by the Nuremberg Code. An *element* of constraint can remain even after coercion has been "minimized" to the extent the circumstances (of, say, imprisonment) allow. Second, EPA's claim that its Rule ensures "comprehension" by human subjects ignores the only evidence on this issue before EPA, which was

Nor is EPA correct that "the issue of legal representatives providing consent on behalf of children . . . is not at issue." EPA Br. 47. EPA has placed such experiments at issue by declining to prohibit pesticide toxicity experiments on children unless the experimenter intends to submit the results for EPA's consideration under FIFRA or FFDCA. *See supra*, at Argument II. In any event, EPA's argument simply highlights the Rule's authorization of pesticide toxicity experiments on persons who are mentally infirm, incapacitated, or imprisoned, if a "representative" provides "consent." EPA defends this chilling proposition by arguing that the Declaration of Helsinki, Common Rule, and Belmont Report do not prohibit consent by a "representative." EPA Br. 47. EPA similarly argued, during the rulemaking, that ethical principles had "evolved," A1277, and that later statements of ethics provided "much more viable guidance" than the Nuremberg Code itself. A1182; *see also* EPA Br. 47. Congress required consistency with the Nuremberg Code, however, and EPA may not discard that Code whenever EPA believes it to be dated. *See* A647 (151 Cong. Rec. H7020 (July 28, 2005)

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the Academy's conclusion that the Common Rule standards that EPA's Rule adopted provide too little guidance to ensure comprehension. A244.

In any event, EPA's rationalizations of how the Rule conforms to the Nuremberg Code's "comprehension" and "without any element of . . . constraint" requirements come too late in the day. Neither explanation was ever articulated by EPA during the Rulemaking. A1277-78. When Petitioner objected that the draft rule failed to ensure full comprehension, for example, EPA ignored the comment. A1180-81. EPA's action "must be upheld, if at all, on the basis articulated by the agency itself" during the Rulemaking, not "counsel's post hoc rationalizations." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 50.

(statement of Rep. Solis) ("This amendment forbids the EPA from considering any intentional human dosing study unless it meets the minimum ethical and scientific safeguards outlined in . . . the 1947 Nuremberg Code adopted after World War II.")).

The Rule also is contrary to FIFRA section 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P), which bars human pesticide experiments without the "fully informed" consent of "such human beings" on whom pesticides are tested. SPA2; Pet'rs. Br. 51-52, 53. Notwithstanding EPA's summary conclusion to the contrary, EPA Br. 48, the Rule obviously allows tests to proceed without the consent of "such human beings" when "consent" is given by a representative. The Rule is contrary to FIFRA section 12(a)(2)(P) and should therefore be set aside. *See* 5 U.S.C. § 706(2)(A).

B. The Rule Contravenes the Nuremberg Code's Requirement that Human Experiments Be Based on Prior Animal Studies

The Nuremberg Code allows human experimentation only if the experiment is "so designed and based on the results of animal experimentation . . . that the anticipated results justify the performance of the experiment." A 529. EPA's Rule, by contrast, authorizes human toxicity experiments without regard to whether they are (or are not) based on prior animal studies.

EPA's response, that it "has access to all *available* laboratory animal studies," simply begs the question. EPA Br. 51 (emphasis added). Neither the

Human Testing Rule nor any other authority cited by EPA actually requires that animal studies be "available" before a human experiment is conducted; EPA's implication that "the animal studies" are "required to be submitted under" the Rule, EPA Br. 51, is thus at best misleading and at worst untrue. Nor does the Rule require, as it should, that human experiments be based on prior animal studies. While EPA *may* review any animal studies that happen to be available, nothing in the Rule directs EPA to do so. A1278 (EPA acknowledgement that its rule does not address Nuremberg Code principle three "directly").

The Nuremberg Code sets forth a clear requirement that EPA's Rule ignores. In lieu of the Code's substantive standard, EPA offers process. Process is not substance, however. Nothing in the Rule directs EPA to ensure consistency with the Code, and EPA could as easily decline to do so. EPA's claim that the Rule's procedures *allow* EPA later to correct the Rule's substantive deficiency falls short.

C. The Rule Ignores the Nuremberg Code's Requirement that Human Experimentation Be Conducted Only When Necessary

The Nuremberg Code's second principle prohibits human experimentation unless the experiment is "such as to yield fruitful results . . . unprocurable by other . . . means of study, and not . . . unnecessary . . . ." A529. EPA's Rule contains no substantively consistent condition. Instead, EPA asserts that it will review experiments to ensure that "[r]isks to subjects are reasonable in relation to anticipated benefits." EPA Br. 52 (alteration in original). The Nuremberg Code's

second principle does not articulate a balancing test, however, but a bright line: Human experiments may not be conducted unless other types of studies cannot procure the information. Because the Rule allows experiments that would violate this principle, the Rule contravenes Section 201.

V. The Court Should Vacate and Remand the Human Testing Rule

This Court should vacate the Human Testing Rule rather than accepting EPA's invitation to leave the Rule in place while EPA revisits its flaws. EPA Br. at 54 n.16. The difference is important. Section 201 imposed a moratorium on EPA's conduct and use of intentional human dosing pesticide toxicity experiments until EPA promulgated a Rule that met certain standards. SPA1. This moratorium is not a "regulatory gap," as EPA suggests, EPA Br. 54 n.16; it is a ban. Petitioners do not "favor" EPA's issuance of a substantively inadequate regulation that lifts that ban on EPA conduct and use of human toxicity experiments.

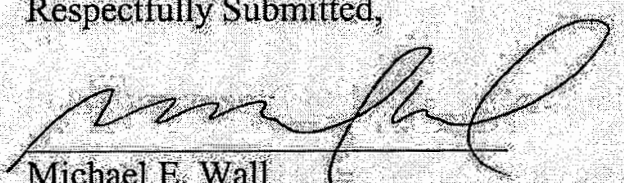
EPA's promulgation of the Human Testing Rule has had real, harmful consequences for Petitioners and their members. In the months after EPA promulgated the Rule, EPA relied on human dosing toxicity experiments to increase allowable pesticide exposure limits and to weaken public health protections. Had EPA *not* promulgated this Rule, the Agency could not have used the human studies to justify these weakened standards. If this Court vacates the

Rule, EPA will be obligated to revisit those standards. Petitioners therefore urge the Court to vacate the Rule at this time.

CONCLUSION

This Court should vacate the Human Testing Rule and direct EPA to issue a new rule in accordance with law.

December 14, 2006 Respectfully Submitted,

By: 

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Certificate of Compliance with Rule 32(a)

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B)(ii) because it contains 6995 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office Word 2003 in a 14 point, Times New Roman font.

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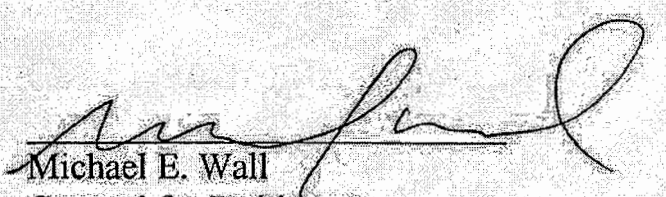

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that she is an employee in the San Francisco Office of the Natural Resources Defense Council, 111 Sutter Street, 20th Floor, San Francisco, CA, 94104; is a person of such age and discretion to be competent to serve papers; and that on December 14, 2006 she served copies of the attached:

- Petitioners' Reply Brief
- Declarations in Support of Petitioners' Standing

by causing said copies to be placed in a prepaid or postpaid envelope addressed to the persons hereinafter named, at the places and addresses stated below, which are the last known addresses, and by either delivering said envelope to Federal Express for delivery or depositing said envelope and contents in the United States Mail at San Francisco, California, or by facsimile, e-mail, or hand delivery, as stated below:

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I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Dated: December 14, 2006

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Appropriations Act language

None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180-days after enactment of this Act.

Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, § 201, Pub. L. 109-54, 119 Stat. 499. (Att. 1)

06-0820-ag(L)

06-1895-ag (CON), 06-2149-ag (CON), 06-2360-ag (CON)

In the United States Court of Appeals for the Second Circuit

Natural Resources Defense Council, Inc., Pesticide Action Network North America, Pineros y Campesinos Unidos Del Noroeste, Physicians for Social Responsibility-San Francisco, Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network,
Petitioners,

v.

United States Environmental Protection Agency,
Respondent.

On Petition for Review of an Order of the
United States Environmental Protection Agency

RESPONDENT'S BRIEF

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November 16, 2006

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JURISDICTIONAL STATEMENT

On February 6, 2006, Respondent United States Environmental Protection Agency ("EPA") issued a final rule, entitled "Protections for Subjects in Human Research" (the "Research Rule"), which Petitioners challenge in these consolidated cases. The Research Rule was promulgated pursuant to Section 201 of the Department of the Interior, Environment and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-54, 119 Stat. 499 (the "Appropriations Act"); Section 408(e)(1)(C) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 346a(e)(1)(C); Sections 3(a) and 25(a) of the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), 7 U.S.C. §§ 136a(a), 136w(a); 5 U.S.C. § 301; and 42 U.S.C. § 300v-1(b). 71 Fed. Reg. 6138, 6168 (Feb. 6, 2006), (SPA4, SPA34).[1]

This Court lacks jurisdiction over these petitions for review because the Petitioners lack standing to bring their challenge. For the reasons explained below, *infra* at 19-29, Petitioners cannot show the requisite injury for constitutional standing because the Research Rule does not subject them to any exposure to pesticides. Further, Petitioners cannot establish standing based upon a speculative chain of events that could lead to a hypothetical injury associated with the possibility of higher pesticide exposure levels that might be established in future EPA proceedings. In addition, Petitioners' alleged injuries are not traceable to the

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[1] References to documents contained in the Special Appendix are cited as "SPA[page number]" and to documents contained in the Appendix as "A[page number]." The Special Appendix and the Appendix were filed by Petitioners on October 4, 2006.

Research Rule because the Rule itself does not establish any less stringent exposure levels for pesticides.

If the Court finds that Petitioners have standing, then this Court has subject matter jurisdiction to review the final agency actions under Section 408(h)(1) of FFDCA, 21 U.S.C. § 346a(h)(1). The petitions for review were timely filed on February 23, 2006, February 24, 2006, and April 6, 2006.

STATEMENT OF ISSUES

1. Whether the petitions should be dismissed because Petitioners have failed to present evidence demonstrating that the Research Rule causes any actual or imminent concrete injury to themselves or their members, or that any alleged injury is traceable to the Research Rule, and thus have failed to demonstrate standing under Article III of the Constitution.

2. Whether the Research Rule, which prohibits third-party research involving intentional exposure of pregnant women, infants or children when that research is intended to be submitted to EPA under FIFRA or FFDCA, satisfies the Appropriations Act's requirement that the Research Rule not permit the use of pregnant women, infants or children as subjects in third-party intentional dosing human toxicity studies for pesticides.

3. Whether the Research Rule, because it is consistent with the principles of respect for persons, beneficence, and justice contained in the 2004 report of the National Academy of Sciences on intentional human dosing (the "NAS Report"), is consistent with the "principles proposed in" the NAS Report.

4. Whether the Research Rule, which *inter alia* extends the requirements for voluntary, fully informed consent to third-party research intended to be submitted to EPA under the pesticide laws, is consistent with the principles of the Nuremberg Code and the requirements of FIFRA.

STATEMENT OF THE CASE

Scientific research with human subjects has provided a great deal of valuable information to help characterize and control risks to public health. EPA believes that, in general, it can best protect public health by considering all available, relevant, scientifically sound information, including, where appropriate, information developed through research with human subjects. 71 Fed. Reg. at 6139 (SPA5). However, research with human subjects has also raised ethical concerns for the welfare of the human participants. The public has long debated the circumstances under which it should be considered ethical to use humans as subjects in research, and when it would be appropriate for the government to rely on the results of ethically problematic research. That debate has intensified in recent years.

In 1991, EPA, along with fourteen other federal departments and agencies, promulgated regulations known as the "Common Rule" to govern the ethical and scientific conduct of research with human subjects conducted or supported by these federal departments or agencies. However, studies not conducted or supported by the federal government ("third-party studies") have generally not been regulated. This regulatory gap was highlighted by EPA's recent receipt and evaluation of certain human studies submitted under FIFRA and FFDCA. In 2005, Congress

included a section in the Appropriations Act directing EPA to undertake additional rulemaking to address third-party intentional dosing human toxicity studies for pesticides.

Section 201 of the Appropriations Act identified several elements for the content of the rule. It directed that the rule not permit the use of pregnant women, infants or children as subjects in such third-party studies. 119 Stat. at 531 (SPA1) It also instructed that the rule be "consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation." 119 Stat. at 531 (SPA1) .

In February 2006, EPA promulgated the Research Rule, which significantly strengthened and expanded protections for subjects of human research. The Research Rule addresses, *inter alia*, two primary topics relevant to this case: (i) it establishes standards for persons conducting studies involving intentional exposure of human subjects intended to be submitted to EPA under FIFRA or FFDCA; and (ii) it establishes standards that govern the use by EPA of such studies under these statutes, regardless of who conducted or sponsored the studies or for what purpose they were conducted.

First, the Research Rule extends the Common Rule requirements previously applicable to studies conducted or sponsored by EPA to third-party studies involving intentional exposure to human subjects that are intended for submission to EPA under FFDCA or FIFRA. It prohibits third parties from conducting intentional dosing studies intended for submission to EPA under FFDCA or FIFRA

with pregnant woman or children as subjects. The Research Rule also places additional restrictions on human research conducted or supported by EPA. It prohibits EPA from conducting or supporting research involving intentional exposure with pregnant women or children as subjects.

Second, the Research Rule sets new standards for EPA's consideration of completed research for pesticides, whether conducted before or after the effective date of the Rule. For example, the Research Rule precludes EPA from relying, in its actions under FIFRA or FFDCA, on any intentional dosing toxicity studies that either involve pregnant women or children as subjects or are otherwise considered unethical, except in narrowly defined circumstances.

Petitioners, who are groups whose purposes include minimizing exposure to pesticides, contend that the Research Rule is not sufficiently stringent. Petitioners' challenges stumble at the Constitutional threshold because Petitioners lack Article III standing. Because numerous, speculative contingencies must occur before any Petitioner could raise an actual controversy or assert an actual injury traceable to the Research Rule, Petitioners cannot demonstrate standing.

If the Court reaches the merits of Petitioners' claims, it will find that EPA reasonably interpreted the provisions of the Appropriations Act in adopting the Research Rule. In light of the context of the Appropriations Act and the regulatory actions Congress sought to address by the Act, EPA reasonably interpreted the requirement that pregnant women, children, and infants not be subjects in "intentional dosing human toxicity studies for pesticides" as applying to studies intended to be submitted to EPA under FIFRA or FFDCA. In addition, given the

pattern of references within the NAS Report to "principles", EPA reasonably interpreted the phrase "principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing" to refer to the principles repeatedly referenced in the NAS Report, rather than the separate, specific recommendations contained in the NAS Report. Finally, the requirements for informed consent and other provisions of the Research Rule are consistent with the principles articulated in the Nuremberg Code and with FIFRA Section 12(a)(2)(P).

I. Statutory and Regulatory Background

A. Pesticide Tolerances under the FFDCA

Section 408(b)(1) of the FFDCA, as amended by the Food Quality Protection Act ("FQPA"), authorizes EPA to establish, by regulation, "tolerances" that set the maximum permissible levels of pesticide residues in or on foods. 21 U.S.C. § 346a(b)(1). EPA may establish regulations setting a tolerance for a pesticide residue or, in appropriate cases, an exemption from the tolerance requirement, only if EPA determines that the tolerance or exemption is "safe." FFDCA section 408(b)(2)(A)(i) & (c)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i) & (c)(2)(A)(i). A finding that a tolerance or exemption is safe must be based on "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." FFDCA section 408(b)(2)(A)(ii) & (c)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii) & (c)(2)(A)(ii).

In amending FFDCA, the FQPA also required EPA to reevaluate the safety of all pesticide tolerances existing at the time of the FQPA's enactment in 1996,

based on a more stringent and scientifically complex evaluation of risk factors. *See* FFDCA section 408(q), 21 U.S.C. § 346a(q). The FQPA mandated that EPA, when calculating safe levels of total exposure for purposes of setting tolerances, apply an additional ten-fold margin of safety (*i.e.*, reducing the level of acceptable exposure by a factor of ten) to account for, *inter alia*, potential pre- and post-natal toxicity unless reliable data show that a different safety factor is safe for infants and children. 21 U.S.C. § 346a(b)(2)(C). Congress required this reassessment, which involves over 9,000 pesticide uses, to be completed within ten years of the FQPA's enactment, which period ended on August 3, 2006. *Id.; see* A23.

B. Sale, Distribution and Use of Pesticides Under FIFRA

Under FIFRA, EPA regulates the sale, distribution, and use of pesticides through a licensing or registration program. Regulation of pesticides under FIFRA and FFDCA is closely linked. Under FIFRA, EPA may not issue a registration for a pesticide that causes "unreasonable adverse effects on the environment." *See* FIFRA section 3(c)(5) & (7), 7 U.S.C. § 136a(c)(5) & (7). That phrase is defined to include "any unreasonable risk to man or the environment" or "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under [FFDCA section 408]." FIFRA section 2(bb), 7 U.S.C. § 136(bb).

Like the FFDCA, FIFRA contains requirements that EPA re-examine existing pesticide registrations to assure that they meet current standards for registration, and the statute contains schedules for doing so. FIFRA section 4, 7 U.S.C. § 136a-1.

With respect to studies involving human subjects, FIFRA makes it unlawful "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test[.]" FIFRA section 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P).

II. Protections for Subjects in Human Research

Human testing to determine the effects of various substances, including pesticides, has been undertaken and the results have been submitted to the United States government for many years. However, for the past several years, EPA has been at the center of an intense debate about the merits and potential use by EPA of human studies submitted under the pesticide laws and about what to do with human studies that are ethically deficient. *See* 71 Fed. Reg. at 6139 (SPA5); A144-46 (NAS Report).

EPA believes it is important to utilize the data available in order to determine the appropriate level of exposure that will satisfy its obligations under FIFRA and FFDCA. EPA's understanding of the potential risks of pesticides to people is usually based on many tests performed with laboratory animals. 71 Fed. Reg. at 6139 (SPA5). Sometimes, however, animal data can provide an incomplete or misleading picture of a substance's safety or risk. *Id.* EPA also has received research involving human subjects, such as epidemiological studies, monitoring studies, and intentional dosing studies, which can provide additional data that is relevant to EPA's determinations under FIFRA and FFDCA. The available data

for a specific pesticide, which may include animal studies as well as human studies, can provide a basis for establishing a more stringent regulatory standard, a less stringent regulatory standard, or maintaining a current regulatory standard. If the data show that a less stringent regulatory standard is appropriate, EPA is complying with its statutory mandates under FIFRA and FFDCA by setting the standard at that level. Even when human research does not show people to be more sensitive than animals, scientifically sound human data developed under strict ethical standards can strengthen the basis for EPA regulatory actions. *Id.; see also* A129 (NAS Report).

A. History of EPA's Human Testing Policy

To ensure the protection of individuals participating as subjects in human testing that EPA conducts or supports, EPA joined other federal departments and agencies in jointly promulgating the "Common Rule" in 1991, codified for EPA at 40 C.F.R. Part 26, Subpart A.[2/] The Common Rule requires that human testing conducted or supported by EPA meet strict ethical and scientific standards. For example, the Common Rule imposes demanding procedures concerning informed and free consent. 40 C.F.R. §§ 26.111(a)(4)-(5), 26.116. In addition, the Common Rule requires, *inter alia*, approval by an Institutional Review Board ("IRB") before human testing begins and continuing oversight thereafter by the IRB. 40 C.F.R. §

[2/] Various agencies involved in human research developed the Common Rule cooperatively. Fourteen other agencies have promulgated regulations comparable to EPA's codification of the Common Rule. *See, e.g.*, 56 Fed. Reg. 28,003 (June 18, 1991) (promulgation of regulations by multiple agencies).

26.103(b). An IRB is a board of at least five members with varying backgrounds and possessing the professional competence, experience and expertise to review adequately research activities presented for its approval. 40 C.F.R. § 26.107(a).[3/]

In 1999, in response to continuing public concerns over human research with pesticides, particularly certain human studies submitted by third parties in support of pesticide actions, EPA convened an advisory committee under the joint auspices of the EPA Science Advisory Board ("SAB") and the FIFRA Scientific Advisory Panel ("SAP"). This advisory committee completed its report in September 2000. A1-67. Although the committee agreed on several broad principles, no clear consensus emerged on many other points, including either the scientific merit or the ethical acceptability of studies to identify or to measure toxic effects of pesticides in human subjects. The public debate continued. *See* A159-60 (NAS Report).

[3/] NRDC incorrectly asserts that EPA has only partially implemented the Common Rule. *See* Pet. Br. at 17, 29 n.10. The Common Rule consists only of the regulations set forth in the document establishing the common Federal Policy for the Protection of Human Subjects as contained in the Federal Register notice of June 18, 1991. *See, e.g.*, 56 Fed. Reg. 28,003, 28,004, 28,012 ("Each of these Departments and Agencies have adopted the common rule as regulations to be codified as listed above."; "The text of the Common Rule ... appears below..."). This policy, which became the Common Rule, was based on Subpart A of the Department of Health and Human Services' ("HHS") regulations; the policy, as concurred in and then adopted by all affected federal departments and agencies, did not incorporate Subparts B, C, and D of HHS' regulations. Thus, those subparts are not part of the Common Rule. *Id.* at 28,004-05. EPA has implemented the Common Rule in its entirety.

In December 2001, EPA requested that the National Academy of Sciences (the "NAS") review scientific and ethical issues concerning third-party intentional dosing studies. 71 Fed. Reg. at 6140 (SPA6). Specifically, EPA asked the NAS to provide advice on the question of whether and, if so, under what circumstances, EPA should accept and consider intentional human dosing studies conducted by third parties to gather evidence relating to the risks of a chemical or the conditions under which exposure to chemicals could be judged safe. A124; *see also* A165-66 (setting forth the specific statement of task).

In response, the NAS issued a lengthy report in 2004. A107-331. The NAS Report endorsed the ethical principles of respect for persons, beneficence and justice. A236. The report made seventeen recommendations to strengthen EPA's oversight of human research and to provide guidance for the use of intentional human dosing studies by EPA. *See* A129-43.

In 2005, Congress addressed the issue of human testing for pesticides. In Section 201 of the Appropriations Act, Congress specified that none of the funds made available by that Act may be used by EPA to "accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject." Pub. L. No. 109-54, Section 201, 119 Stat. at 531 (SPA1). Congress further provided that such rule "shall not permit the use of pregnant women, infants or children as subjects [and] shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code

with respect to human experimentation." *Id.* The Appropriations Act also required that the rule establish an independent Human Subjects Review Board. *Id.* Finally, the Appropriations Act required that the rule be promulgated no later than 180 days after enactment of the Appropriations Act. *Id.*

EPA promulgated the Research Rule on February 6, 2006, culminating several years of agency deliberations and meeting the requirements of the Appropriations Act. The Research Rule strengthens and expands protections both for research conducted or supported by EPA and for "third-party" intentional exposure human research and intended for submission to EPA under FIFRA or FFDCA. First, with respect to research supported or conducted by EPA, the Research Rule categorically prohibits any research involving intentional exposure of pregnant women or children and adopts additional protections, beyond those of the Common Rule or required by the Appropriations Act, for pregnant women and children who are subjects in observational research supported or conducted by EPA. 71 Fed. Reg. at 6138 (SPA4); 40 C.F.R. Subparts B, C, & D.

Second, with respect to third-party research, the Research Rule: (1) prohibits new research involving intentional exposure of pregnant women or children that is intended for submission to EPA under the pesticide laws; (2) extends the provisions of the Common Rule, including provisions requiring voluntary informed consent and additional safeguards for certain vulnerable subjects, to other human research involving intentional exposure of non-pregnant adults that is intended for submission to EPA under the pesticide laws; (3) requires the submission to EPA of protocols and related information about any human

research before it is initiated so that EPA can review that information to ensure, *inter alia,* that risks to human subjects are minimized; and (4) establishes an independent Human Studies Review Board ("HSRB") to review both proposals for new research and reports of covered completed human research on which EPA proposes to rely in any action under the pesticide laws. *Id.*

The Research Rule also defines the criteria EPA will use to determine whether to rely upon human research involving intentional exposure in its actions under the pesticide laws. For example, the Research Rule generally forbids EPA to rely in its actions under the pesticide laws: (1) on research conducted at any time involving intentional exposure of pregnant women or children as subjects; (2) on research initiated before the effective date of the Research Rule involving intentional exposure of non-pregnant adults that is fundamentally unethical or "significantly deficient relative to standards prevailing" when such study was conducted; or (3) on research initiated after the effective date of the Research Rule involving intentional exposure of non-pregnant adults that fails substantially to comply with the requirements of the Research Rule. 40 C.F.R. §§ 26.1703, 26.1704, 26.1705 (SPA42). The only exception to these prohibitions applies if reliance on the otherwise unacceptable research would be crucial to a decision to impose a more stringent regulatory restriction that would improve protection of public health than could be justified without relying on the research, and then only after EPA obtains the views of the HSRB and fulfills certain public notice and comment requirements. 40 C.F.R. § 26.1706 (SPA42).

STANDARD OF REVIEW

Assuming for purposes of argument that the Court may reach the merits of this dispute, judicial review under FFDCA is governed by the standards set forth in the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 551-559, 701-706, which establishes a highly deferential standard of review for agency action. Such action is valid unless it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

This Court has held that "review under this provision is narrow, limited to examining the administrative record to determine whether the [agency] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Riverkeeper, Inc. v. EPA*, 358 F.3d 174, 184 (2d Cir. 2004) (citations and internal quotes omitted); *see also NRDC v. Muszynski*, 268 F.3d 91, 97 (2d Cir. 2001) (same). The Court "may not substitute its judgment for that of the agency[.]" *Muszynski*, 268 F.3d at 97 (citation and internal quotation omitted). Rather, the Court should affirm EPA's decision unless EPA has:

> relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Id. (citation and internal quotations omitted). In short, this standard of review presumes the validity of agency action, *Ethyl Corp. v. EPA*, 541 F.2d 1, 34 (D.C. Cir. 1976) (*en banc*), and if the agency's reasons and policy choices conform to "certain minimal standards of rationality," the action is reasonable and must be

upheld. *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 521 (D.C. Cir. 1983).

With regard to questions of statutory interpretation, this Court must first consider whether Congress has directly addressed the question at issue. If so, "that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837, 842-43 (1984). However, "if the statute is silent or ambiguous with respect to the specific issue, the question for the Court is whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843. To uphold EPA's interpretation of Section 201 of the Appropriations Act, the Court need not find that EPA's interpretation is the only permissible construction that EPA might have adopted, but only that EPA's interpretation is reasonable. *See Chevron*, 467 U.S. at 844; *Chemical Mfrs. Ass'n v. NRDC*, 470 U.S. 116, 125 (1985); *Sutherland v. Reno*, 228 F.3d 171, 173 (2d Cir. 2000) ("when reviewing an agency determination, federal courts must accord substantial deference to an agency's interpretation of the statutes it is charged with administering.")

When an agency's decision rests on an evaluation of complex scientific data within the agency's technical expertise and judgment, courts are "extremely deferential." *New York v. Reilly*, 969 F.2d 1147, 1152 (D.C. Cir. 1992); *see also Browning-Ferris Indus. of S. Jersey, Inc., v. Muszynski*, 899 F.2d 151, 160 (2d Cir. 1990). The court "must look at the decision not as the chemist, biologist, or statistician that [it is] qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to

certain minimal standards of rationality." *Ethyl Corp.*, 541 F.2d at 36; s*ee also* *Riverkeeper*, 358 F.3d at 184 (this Court "lack[s] the EPA's expertise when it comes to scientific or technical matters"). EPA recognizes that, in this case, it has not drawn conclusions about specific scientific studies and the extent to which they would support a given action; however, in developing the Research Rule, and particularly in defining the scope of the Rule's applicability to third-party intentional exposure studies, EPA did apply its considerable knowledge about the many kinds of research with human subjects, how they are conducted, in what circumstances they might be relevant, and how they might be used. All these considerations are relevant to the choice of scientific and ethical standards that govern decisions to accept or rely on research with human subjects. Accordingly, the basic principle of deference articulated in *Ethyl* and *Riverkeeper*, which strives to respect the Agency's expertise in matters concerning scientific decisionmaking, should apply here.

SUMMARY OF ARGUMENT

Petitioners lack standing to challenge the Research Rule. Petitioners assert injury based upon a risk of increased exposure to pesticides. However, Petitioners do not allege that their members volunteer to be subjects in human research, so the Research Rule does not change their exposure to pesticides. The "risk" that the Research Rule may influence the availability of information on which EPA may rely in separate administrative actions under FIFRA or FFDCA to establish safe levels for pesticides is not an actual or imminent injury sufficient for standing. Moreover, because the Research Rule does not establish any less stringent safety levels for pesticides, it cannot be the cause of Petitioners' alleged injuries.

If the Court determines that Petitioners have standing, the Court should find that EPA complied with Congress' direction not to permit the use of pregnant women or children as subjects in third-party intentional dosing human toxicity studies for pesticides. EPA reasonably interpreted the phrase "studies for pesticides" to refer to studies intended to be submitted to EPA under the pesticide program, which is governed by FFDCA and FIFRA. This interpretation reflects the context and purpose of Section 201 of the Appropriations Act, which was enacted against the backdrop of human studies that had been submitted for use in EPA's ongoing risk assessments pursuant to FIFRA and FFDCA. Congress was concerned with EPA's use of third-party intentional human dosing studies in its regulatory activities for pesticides, not with studies published in scientific journals or for state or foreign regulatory purposes. Therefore, EPA reasonably interpreted

the scope of the prohibition on using pregnant women, infants and children as concerning those studies submitted to it under FIFRA and FFDCA.

EPA also complied with the congressional direction to promulgate a rule consistent with the "principles proposed" in the NAS Report. EPA identified the principles articulated in the NAS Report – respect for persons, beneficence, and justice – and ensured that the Research Rule is consistent with each of those three principles. Petitioners instead contend that the Research Rule must be consistent with the seventeen specific recommendations presented in the NAS Report, notwithstanding the fact that the Appropriations Act makes no mention of the NAS recommendations. Even if the Court were to find Petitioners' alternative interpretation of the Appropriations Act plausible, that would not make EPA's reading of "principles" unreasonable.

The Research Rule is also consistent with the principles of the Nuremberg Code. The phrase "consistent with" is flexible statutory language and does not require an exact correspondence but only compatibility. The Research Rule's provisions for informed consent, which include consent by legal representatives, is compatible with the Nuremberg Code's principles. Petitioners' other arguments based upon the Nuremberg Code reflect the fact that EPA did not incorporate in full the exact language of the Nuremberg Code, but instead used language consistent with the Nuremberg Code principles. For example, Petitioners complain that the Research Rule does not ensure that the subject will have "sufficient knowledge and comprehension" of the matter because the rule requires that the information given to the subject be "in language understandable to the subject."

EPA's choice of words in this instance, and in the other instances argued by Petitioners, incorporate this Nuremberg Code principle, and the lack of exact replication of the Nuremberg Code's language does not make the Research Rule inconsistent with the Nuremberg Code.

Finally, the existence of studies undertaken by third parties prior to promulgation of the Research Rule that Petitioners find ethically or scientifically suspect provides no basis to find the Research Rule arbitrary or capricious. These third-party studies were conducted when EPA had no regulations governing their conduct. For example, before promulgation of the Research Rule, there were no applicable regulatory requirements specifying the components of informed consent in third-party studies. As discussed below, following promulgation of the Research Rule, study sponsors can no longer represent pesticides as drugs or fail to disclose that a study involves pesticides. EPA's promulgation of the Research Rule reasonably addresses congressional concerns about third-party intentional dosing studies of pesticides with human subjects.

ARGUMENT

I. Petitioners Lack Standing to Challenge the Research Rule.

Courts must resolve jurisdictional issues before considering the merits of a dispute. *See Steel Co. v. Citizens for a Better Env't*, 523 U.S. 83, 94 (1998) (jurisdictional issues should be assessed at threshold; if jurisdiction is lacking, case should be dismissed without further inquiry); *Alliance for Envtl. Renewal,*

Inc. v. Pyramid Crossgates Co., 436 F.3d 82, 85 (2d Cir. 2006). The Court lacks jurisdiction over these petitions because Petitioners have not established standing.[4/]

The "case or controversy" requirement set forth in Article III of the Constitution requires a petitioner to establish standing in order to invoke federal jurisdiction. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992). To meet the Article III requirements for standing, each Petitioner must demonstrate that: (1) it or one of its members has suffered an "injury in fact" that is actual or imminent, not conjectural or hypothetical; (2) the injury complained of is caused by or fairly traceable to the challenged action of EPA; and (3) it is likely that the injury will be redressed by a favorable decision. *See id.* at 560-61; *Lafleur v. Whitman*, 300 F.3d 256, 269 (2d Cir. 2002). The burden is on the Petitioners to demonstrate affirmatively and clearly that they possess sufficient standing to seek the requested relief. *See FW/PBS, Inc. v. City of Dallas*, 493 U.S. 215, 231 (1990); *Lafleur*, 300 F.3d at 268.

As explained above, the Research Rule sets standards for research involving intentional exposures of non-pregnant adults who voluntarily agree to be subjects in the research. Petitioners have not demonstrated that any of their members

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[4/] EPA previously filed a motion to dismiss based on Petitioners' lack of standing. *See* EPA's Motion to Dismiss for Lack of Jurisdiction (Standing), filed June 21, 2006, and EPA's Reply in Support of Motion to Dismiss for Lack of Jurisdiction (Standing) filed August 16, 2006. On August 31, the Court denied the motion "without prejudice to pursuit of the EPA's claims regarding standing before this Court's merits panel."

volunteer to participate in this research. Therefore, the Research Rule does not subject them to any exposure to pesticides.

The alleged injury on which Petitioners rely for standing is a potential increase in exposure to pesticides associated with separate, subsequent administrative actions taken by EPA. This potential "risk" – that the Rule challenged by Petitioners may affect the data available for consideration in future agency decisions addressing exposure to potentially harmful products or substances – is not a risk previously recognized by this or other courts as injury sufficient to establish standing. Further, the Research Rule cannot be shown to be the cause of Petitioners' alleged injury. Accordingly, the Court must dismiss the petitions for lack of jurisdiction.

A. The Petitioners Have Not Suffered an Injury-in-Fact Because the Research Rule Does Not Expose Petitioners' Members to Pesticides.

To demonstrate injury sufficient for standing, a party must show an "injury-in-fact" -- an "invasion of a legally protected interest which is (a) concrete and particularized" and (b) "actual or imminent, not 'conjectural' or 'hypothetical.'" *Lujan*, 504 U.S. at 560; *Lafleur*, 300 F.3d at 269. "Abstract injury is not enough"; the injury must be "real and immediate." *Los Angeles v. Lyons*, 461 U.S. 95, 101-02 (1983).

Petitioners argue that an exposure to alleged potential increased levels of pesticides resulting in an increased risk of injury is sufficient to establish injury-in-fact for Article III standing purposes. Petitioners' Brief ("Pet. Br.") at 3; *see Baur v. Veneman*, 352 F.3d 625, 633-34 (2d Cir. 2003). However, Petitioners' members

will not be exposed to increased levels of pesticides because of the Research Rule. The only exposures to pesticides attributable to the Research Rule are those experienced by volunteers who give their informed consent to be subjects in human testing. Petitioners do not claim that any of their members are exposed to pesticides as a result of being subjects in intentional dosing studies. Thus, the Research Rule does not expose Petitioners' members to pesticides at all, much less increase their exposure.

This fact distinguishes this challenge to the Research Rule from the several cases involving exposure to pollutants that Petitioners cite in their brief. *See* Pet. Br. at 3-4. In each of these cases, the challenged agency action exposed petitioners to pollutants or harmful products. For example, in *LaFleur v. Whitman*, 300 F.3d 256 (2d Cir. 2002), the challenged action allowed issuance of an air emission permit to a facility that emitted sulfur dioxide. The Court found that the petitioner, who worked adjacent to the facility, would likely breathe those emissions, so would likely be exposed to sulfur dioxide. *Id.* at 270. In *New York Public Interest Research Group v. Whitman*, 321 F.3d 316 (2d Cir. 2003), the challenged EPA decision regulated emissions of air pollutants from several facilities. The petitioners' members resided in close proximity to the regulated facilities, and the Court found standing based upon potential exposure to excess air pollution. *Id.* at 325. Finally, in *Baur v. Veneman*, the challenged livestock regulation authorized human consumption of downed cattle, which had a higher chance of transmitting disease. 352 F.3d at 628. Mr. Baur ate beef, which could have come from downed

cattle as the result of the regulation, and the Court therefore found standing based on exposure to potentially unsafe food products. *Id.* at 636, 640.

In contrast, Petitioners are not claiming that any of their members inhale or ingest pesticides in human research studies. Thus, Petitioners and their members are not injured by exposure to pesticides as a result of the Research Rule.

1. Petitioners' Members' Alleged Injuries Cannot Occur Until and Unless EPA Takes Subsequent Administrative Action That Increases Petitioners' Members' Exposure to Pesticides.

Petitioners cannot base standing on the possibility that study data not prohibited by the Research Rule will be used in an extended chain of contingent government actions to increase their exposure to pesticides. Although Petitioners attempt to characterize this injury as an increased risk of harm due to higher pesticide exposures, the "risk" they actually face is an increased chance that *future* agency action could result in increased exposures to pesticides. This is not an actual, concrete injury, but an allegation based upon an extended chain of speculation as to future events.

Courts have rejected, for standing purposes, injury attributable to the increased likelihood of subsequent adverse government decisions. In such cases, the injury does not occur unless and until the future government decision is made. *See Louisiana Envtl. Action Network v. Browner*, 87 F.3d 1379, 1383 (D.C. Cir. 1996) ("*LEAN*") (petitioners' assertions too remote to establish imminent and concrete injury because petitioners could not be injured without occurrence of subsequent chain of events that might not come to pass); *Shoreham-Wading River*

Cent. School Dist. v. NRC, 931 F.2d 102, 105 (D.C. Cir. 1991) (even if court assumes risks associated with future agency action, any injury could not occur until agency took future action); *cf. Baur*, 352 F.3d at 640 (finding standing where risk was "not a future risk that awaits intervening events.")

Administrative decisions EPA has already made or those it may make subsequent to promulgation of the Research Rule do not provide Petitioners with the standing they otherwise lack. Petitioners' declarations assert that EPA, following promulgation of the Research Rule, took or proposed to take actions that raise pesticide exposure levels for certain pesticides. *See, e.g.*, Declarations of Adam M. Finkel, Sc.D; Beth Koh; Gina Solomon, M.D. M.P.H., filed August 3, 2006. Petitioners further assert that this change is attributable to EPA's consideration of human studies. *Id.* These post-filing events simply confirm the existence of the numerous subsequent contingent steps that must be taken prior to any increased exposure on which Petitioners rely for injury.

The path from promulgation of the Research Rule to Petitioners' members' alleged increased exposure to pesticides requires that, as a result of the Research Rule: (1) a researcher has engaged in a study involving intentional exposure of human subjects that yields data that could support a less restrictive regulatory standard for a pesticide; (2) EPA determines that the study was conducted ethically and was scientifically valid; (3) EPA relies upon the study in a future action to establish or maintain a less restrictive regulatory standard under FFDCA or FIFRA; (4) such standard would not be supported by other data considered by EPA during the decisionmaking process; and (5) one of Petitioners' members is then

exposed to a higher level of pesticides as allowed by the standard. The declarations and documents submitted by Petitioners related to recent EPA actions regarding tolerance levels demonstrate that this multi-step path was followed in the post-Research Rule EPA actions cited by Petitioners. *See, e.g.*, Koh Decl., Exhibits C - H.

In this case, as in *LEAN* and *Shoreham-Wading*, Petitioners' members' alleged injury will occur, if at all, only as a result of a number of agency actions independent of the Research Rule. If EPA sets an exposure level for a particular pesticide under FFDCA or FIFRA that adversely impacts Petitioners, Petitioners may seek to challenge that specific subsequent action. *See LEAN*, 87 F.3d at 1384. The outcome of such subsequent agency decisions does not, however, give Petitioners standing to challenge the Research Rule.

2. Any Alleged Injury to Petitioners' Organizational Interests is Insufficient to Provide Them With Standing to Challenge the Research Rule.

Petitioners also seek to establish organizational injury but, as with their arguments on behalf of their members, they only identify injuries attributable to increased exposure to pesticides. For the reasons discussed in the prior section, the Research Rule itself does not result in the increased levels of exposure to Petitioners' members to pesticides. Thus, Petitioners fail to establish organizational injury.

B. The Petitioners Cannot Satisfy the Causation Requirements of Standing.

Petitioners identify no injury caused by the Research Rule. The "causation" element of constitutional standing requires this Court to ask whether it is "substantially probable" that the challenged action of EPA caused the Petitioners' alleged particularized injury. *See Florida Audubon Soc'y v. Bentsen*, 94 F.3d 658, 663 (D.C. Cir. 1996) (en banc). The Research Rule does not establish less stringent safety levels for pesticides. Further, the Research Rule contains no determination regarding the scientific validity and probative value of specific human research involving pesticides. The Research Rule does not require EPA to rely on any human studies. Because the Research Rule does not authorize pesticide exposures (other than to subjects of research), the pesticide exposures on which Petitioners base their injury are not traceable to the Research Rule.

This lack of causation in the circumstances of this case is entirely consistent with *Baur v. Veneman*. The regulation reviewed in *Baur* authorized the use of downed livestock for human consumption notwithstanding Mr. Baur's claims of disease transmission. 352 F.3d at 637-38. Finding that Mr. Baur's potential consumption of downed livestock constituted an injury-in-fact, the Court then found that the injury "arises directly from the USDA's regulatory policy of permitting the use of downed cattle for human consumption." *Id.* at 640. No subsequent agency action was required to cause the injury. The *Baur* decision did not address a challenge to an agency action that does not itself authorize the exposures that Petitioners claim could cause them injury.

Petitioners are in no different position than the petitioners in *Shoreham-Wading*, who sought to challenge an agency ban on refueling a nuclear reactor by arguing that the ban laid the basis for future agency action that could pose environmental risks.[5] Here, Petitioners claim the Research Rule lays the basis for future agency action that could increase their exposure to pesticides. That claim is insufficient to establish that their injury is fairly traceable to the Research Rule. *See Natural Resources Def. Council v. EPA*, 902 F.2d 962, 976 (D.C. Cir. 1990) (affected parties can contribute to future regulatory action and, if future action is based on poor information, it could be challenged by affected parties).[6]

C. Even if the Court Finds That Petitioners Have Established Injury Based on an Increased Risk of Exposure, Petitioners Do Not Have Standing to Pursue Their First Issue on Review.

Even if the Court finds that Petitioners have standing based upon their claim of injury attributable to potentially less stringent exposure levels set by EPA as a result of the use of human studies, they still cannot establish standing to pursue

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[5] In *Shoreham-Wading River Central School Dist. v. NRC*, 931 F.2d at 105, the court observed that, even if it assumed the risks associated with the future action, any injury could not occur until the agency took the future action. In other words, even if the ban was a "but for" cause of a future agency action and any resulting risk, the future action will be the operative cause of injury. *Id.* The petitioners in *Shoreham-Wading* could not establish that the environmental risks were fairly traceable to the refueling ban.

[6] The Supreme Court's decision in *Bennett v. Spear*, 520 U.S. 154 (1997), is not apposite. In *Bennett*, the Court found standing to challenge a Fish and Wildlife Service biological opinion that was "virtually determinative" of the subsequent Bureau of Reclamation decision. *Id.* at 170. In this case, the Research Rule makes no determinations regarding any safety levels for any pesticides.

their first issue on review. As their first issue, Petitioners challenge EPA's interpretation of a portion of Section 201 to prohibit third-party studies involving intentional exposure of pregnant women and children that are intended for submission to EPA under FIFRA or FFDCA. Petitioners claim that the statutory language should have been interpreted to include *all* human toxicity studies involving pesticides in any way, such as studies done for publication, for submission to state agencies or foreign authorities or for submission to EPA under other federal environmental statutes. Pet. Br. at 24. However, Petitioners have not articulated any injury attributable to this allegedly unlawful statutory interpretation.

To establish injury, Petitioners' declarations rely exclusively on risks of exposure to higher levels of pesticides resulting from EPA consideration of the results of human studies in establishing exposure levels for pesticides in an action under FIFRA or FFDCA. Pet. Br. at 3.[7] The Research Rule at section 26.1703 prohibits EPA reliance on any research involving intentional exposure of pregnant women or children in any action under FIFRA and FFDCA, without regard to who may have conducted the underlying research, when it was conducted, with what intent it was conducted, or how it came into the hands of EPA. Thus, the scope of the prohibition on EPA's reliance on studies involving pregnant women, children

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[7] *See* Declarations of Adam M. Finkel, Sc.D; Harjinder S. Gill; Beth Koh; Karen Mountain; Stacy Justus Nordgren; Ramon Ramirez; Margaret Reeves, Ph.D; Rhonda Roff; Gina Solomon, M.D. M.P.H.; Gina Trujillo; and Baldemar Velasquez. These declarations were filed August 3, 2006.

and infants is broad enough to avoid Petitioners' articulated injury of increased risk of less stringent standards under FIFRA or FFDCA.

Petitioners identify no injury attributable to risks of exposure associated with other uses of studies. Petitioners do not demonstrate how they are injured by the *publication* of an intentional exposure study involving pregnant women, children, or infants. Similarly, they have not identified any action by a foreign country or state that, as a result of considering studies involving these sensitive populations, will result in an increase in their exposure to pesticides. Nor have they identified any EPA action under other federal environmental statutes that, through consideration of studies involving these sensitive populations, will injure them. For example, none of them alleges that they reside near a hazardous waste site or a polluted water body from which exposures to pesticides will increase due to EPA's future consideration of unspecified future studies involving pregnant women or children. *See Lujan*, 504 U.S. at 565-66 (a "plaintiff claiming injury from environmental damage must use the area affected by the challenged activity"). Therefore, Petitioners lack standing to assert that the Research Rule should have covered all human studies.

II. EPA Reasonably Interpreted the Appropriations Act to Preclude Intentional Dosing Human Toxicity Studies Using Pregnant Women, Infants or Children as Subjects When the Studies Are Intended to be Submitted to EPA under FIFRA and FFDCA.

Section 201 of the Appropriations Act states that the Research Rule "shall not permit the use of pregnant women, infants or children as subjects" in "third-party intentional dosing human toxicity studies for pesticides." The Research Rule contains such a prohibition. It prohibits third-party research involving intentional exposure of human subjects who are pregnant women or children when the research is intended to be submitted to EPA under FFDCA or FIFRA. 40 C.F.R. § 26.1203 (SPA40). EPA reasonably interpreted the phrase "studies for pesticides" to address those studies intended for submission to EPA under FIFRA or FFDCA.

Petitioners argue that the phrase "studies for pesticides" is susceptible to only one meaning and, therefore, this case should be decided in their favor at *Chevron* step one. Pet. Br. at 27-31. In the light shed by traditional tools of statutory construction, however, the phrase "studies for pesticides" is susceptible to more than one meaning. Moreover, the better alternative reading is EPA's.

The plainness or ambiguity of statutory language is determined by reference to the language itself, the specific context in which that language is used and the broader context of the statute as a whole. *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997). The meaning of a statute is determined not only by the particular statutory language, but the design of the statute and its object and policy. *Crandon v. United States*, 494 U.S. 152, 158 (1990). This Court has instructed that the "appropriate methodology to employ in interpreting a statute is to look to the

common sense of the statute, to its purpose, to the practical consequences of the suggested interpretations, and to the agency's own interpretation for what light each might shed." *Johnson v. United States by the Dep't of Treasury*, 123 F.3d 700, 702-03 (2d Cir. 1997).

In the case of Section 201, the broader context of the statute, including its purpose and policy, demonstrates the reasonableness of EPA's statutory construction. Section 201 was enacted against a backdrop of controversy over the use of human studies as part of EPA's ongoing risk assessments associated with its mandated re-evaluation of over 9,000 pesticide tolerances and hundreds of pesticide re-registrations pursuant to the FQPA. *See generally* A23 (over 9,000 current pesticide tolerances must be reassessed); A125 ("The primary impetus for EPA's request [that NAS provide advice on EPA's use of intentional human dosing studies] was a series of events involving agricultural pesticides and EPA's implementation of the 1996 Food Quality and Protection Act (FQPA)."); A153-58 (NAS Report summary of events that prompted the study). The concerns emphasized by Petitioners in their brief and declarations, as well as by the NAS and EPA's Joint Science Advisory Board/Science Advisory Panel Committee ("SAB/SAP Committee"), arose from the potential use of human studies in connection with the ongoing FFDCA and FIFRA actions, and the fear that EPA's reliance on human studies could lead to less stringent regulatory standards. *See, e.g.*, Pet Br. at 6 ("EPA has nonetheless relied on [ethically troubling] studies to increase exposure limits to pesticides"); A153-55, A164 (NAS Report); A24 (SAB/SAP Committee Report). Specifically, the FQPA instructed EPA to add an

extra safety factor to account for exposures of infants and children to pesticides. 21 U.S.C. § 346a(b)(2)(C). EPA, Petitioners, the SAB/SAP Committee report, and the NAS Report all recognized that pesticide registrants may advocate the use of human studies to reduce the safety factors employed to set the revised or new safety levels for pesticides exposure limits. Pet. Br. at 6; A154-56 (NAS Report); 71 Fed. Reg. at 6161 (SPA27); A24 (SAB/SAP Committee Report).[8/]

As EPA undertook the process of performing risk assessments and setting tolerance levels, it lacked any formal rules governing the consideration of third-party intentional dosing human studies being submitted under FFDCA and FIFRA.

Prompted by EPA's lack of standards in this area, Congress adopted Section 201. It first prohibited EPA from accepting, considering or relying on third-party intentional dosing human toxicity studies for pesticides until EPA issued a final rule on the subject. This prohibition was obviously directed at use of human studies in EPA's ongoing FIFRA and FFDCA actions. The managers of the Appropriations Act noted "the many concerns expressed on both the House and Senate floors with respect to intentional human toxicity dosing studies relied upon by the EPA *in reviewing applications for pesticide approvals*." H.R. Rep. No. 109-188, at 1115 (2005); *see also* 151 Cong. Rec. H6562, H6594 (July 26, 2005) (emphasis added). In the next sentence of the Conference Report, the managers

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[8/] For example, interested persons could argue that when a human study is used as the point of departure for calculating a reference dose or similar standard, the ten-fold interspecies uncertainty factor generally used to account for differences in animals and humans could be reduced or eliminated. *See* A154-55 (NAS Report).

stated that this "[c]oncern is particularly acute for pregnant women, fetuses and children." *Id.* Congress then instructed in the Appropriations Act that "*[s]uch rule* . . . not permit the use of pregnant women, infants or children as subjects." SPA1 (emphasis added). EPA reasonably construed this prohibition as similarly referring to the rule that addresses uses associated with reviewing applications for pesticide approvals, *e.g.*, actions under FIFRA or FFDCA.

EPA's interpretation is supported by the legislative history. The congressional debate that resulted in the passage of Section 201 focused on human subjects research related to EPA actions under FIFRA and FFDCA. Representative Solis expressed her concern that "[c]urrent practices also allow the EPA to accept studies from the pesticide industry and other outside sources so these studies can be used to help develop regulations or approve pesticides." 151 Cong. Rec. H3651, H3671 (May 19, 2005). Similarly, Senator Boxer argued for adoption of Section 201 by referring to human studies that were being submitted to EPA for purposes of regulatory decisionmaking under FIFRA and FFDCA, and her belief that EPA should not be using these studies to avoid the FQPA safety factor. 151 Cong. Rec. S7551, S7552-56 (June 29, 2005).

There is no reason to believe that Congress was concerned about studies being performed for publication in professional journals, for supporting state or foreign regulatory actions, or for submission to EPA under other federal environmental statutes.[9] Neither Representative Solis nor Senator Boxer, nor any

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[9] Contrary to Petitioners' allegations, Pet. Br. at 28 n.8, prior to the enactment of the Appropriations Act and the promulgation of the Research Rule, there was no

of the other proponents of the legislation, mentioned such concerns. The use, sale and distribution of pesticides and residues of pesticides on food in the United States are regulated by EPA under FIFRA and FFDCA. It is therefore reasonable for EPA to interpret the scope of the "studies for pesticides" about which Congress was concerned to be those studies intended for submission to EPA under FIFRA or FFDCA.[10/]

Congress' use of the language "studies *for* pesticides," rather than studies "with" or "on" pesticides further supports EPA's interpretation. A substance is a pesticide not by virtue of its intrinsic properties, but because the substance is intended for a pesticidal purpose. *See* FIFRA § 136(u) ("substance ... intended for preventing, destroying, repelling, or mitigating any pest..."); 40 C.F.R. §§ 152.3,

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reason to suspect that such studies might be conducted to avoid regulatory requirements. As EPA explained in its Opposition to Petitioners' Motion to Complete the Record, Petitioners rely on a reference in a document to "laundering" of studies where there is no such evidence that such practices were or are taking place. EPA Opposition, filed October 16, 2006, at 14-15.

[10/] Petitioners argue that the prohibition on third-party research involving intentional exposure of pregnant women or children as subjects should be broader. Pet. Br. at 27-31. Yet, even if EPA had the authority to ban such research universally, such a ban could have devastating social consequences. For example, many international public health organizations have tested the efficacy of pesticide-impregnated bed-nets in prevention of childhood malaria in Africa, South Asia, and other areas where malaria is endemic and takes the lives of hundreds of thousands of children each year. These studies have shown that as much as 50% of childhood deaths from malaria can be prevented by use of pesticide-impregnated bed-nets. The Research Rule forbids EPA to rely on these studies in its actions because they involve intentional exposure of children, but the Research Rule does not forbid the conduct of these valuable studies because they are not intended for submission to EPA under the pesticide laws.

152.15. If a substance is claimed to be a pesticide, it is subject to regulation under FIFRA and, if it has food or feed uses, under FFDCA. Congress, by specifying that the Research Rule should address studies *for* pesticides signaled its focus on those statutes that regulate pesticides, namely FIFRA and FFDCA.[11/]

Moreover, even if this Court were to find that other potentially reasonable interpretations of the Appropriations Act language exist, it does not make EPA's interpretation unlawful. *See Chevron*, 467 U.S. at 844 (the Court need not find that EPA's interpretation is the only permissible construction that EPA might have adopted, but only that EPA's interpretation is reasonable); *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 409 (1993) (where agency's interpretation is at least as plausible as competing ones, there is little, if any reason, not to defer to its construction). Similarly, EPA's interpretation of this statutory language in an internal guidance document addressing a separate issue does not make its final rulemaking decision unreasonable. Petitioners reference in their brief a guidance document they seek to add to the record, which was prepared by EPA staff to address the Appropriation Act's prohibition against EPA accepting, considering or relying on any third-party intentional dosing human toxicity studies for pesticides

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[11/] EPA's interpretation does not create a loophole that would allow persons to circumvent the scope of the Research Rule for studies submitted under other federal environmental regulatory programs. For purposes of determining a persons' intent to submit a study to EPA under FIFRA or FFDCA, the Research Rule creates a presumption that any study submitted to any office of EPA (not just the office with FIFRA and FFDCA regulatory responsibility) or any study submitted by a person whose products are regulated under FIFRA and FFDCA is presumed to have submitted the study with the requisite intent that would trigger coverage under the Research Rule. 40 C.F.R. § 26.1101(g) (SPA36).

prior to its promulgation of a rule on this subject. Pet. Br. at 31 n.12.[12/] EPA's purpose in drafting this guidance was to assist staff in avoiding potential violations of the Appropriations Act while a rule was being promulgated. As a result, the definitions used in the internal interim guidance were intentionally drafted broadly so as to avoid inadvertent noncompliance with any potential interpretation of the statutory language. The fact that these definitions were, in some instances, broader than either those contained in the proposed rule or subsequently adopted in the final Research Rule following EPA policy development and notice and comment proceedings does not make EPA's interpretation in the Research Rule unreasonable.

Accordingly, EPA's interpretation is entitled to deference and must be upheld.

[12/] EPA disagrees that this document belongs in the record for the Research Rule. *See* EPA's Opposition to Petitioners' Motion to Complete the Administrative Record at 6-8.

III. The Research Rule is Consistent With the Principles Proposed in the NAS Report.

Congress provided that the Research Rule "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing." Congress chose to instruct EPA to issue a rule consistent with the NAS Report's "principles." The NAS Report discusses principles in several locations, and EPA reasonably identified the principles contained in the NAS Report as being respect for persons, beneficence and justice. The Research Rule is consistent with those principles. Petitioners' argument that EPA should have instead focused upon consistency with the seventeen "recommendations" of the NAS Report is contrary to the language of the statute and, in any event, does not undercut the reasonableness of EPA's construction.

The language of the Appropriations Act required EPA to issue a rule consistent with the "principles proposed" in the NAS Report. Congress said "principles," not "recommendations." A "principle" is a "general or fundamental truth" or a "fundamental law, doctrine, or assumption on which others are based or from which others are derived." Webster's Third New International Dictionary of the English Language 1803 (1966). Recommendations can be based upon principles, but a recommendation is not a principle. Under *Chevron* step one, the Court must give effect to the unambiguously expressed intent of Congress.

Even if the Court finds the term "principles" ambiguous, EPA's interpretation of "principles" to refer to those items that the NAS Report calls principles is reasonable. When Congress passed the Appropriations Act in 2005,

it obviously was aware of the NAS Report published in 2004, and knew it contained seventeen specific recommendations that were, in fact, styled as "recommendations." Further, in other statutes, Congress has demonstrated its ability to require that a rule be consistent with NAS "recommendations" when that was its intent. *See Nuclear Energy Inst., Inc. v. EPA*, 373 F.3d 1251, 1267 (D.C. Cir. 2004) (Energy Policy Act required EPA to promulgate standards "based upon and consistent with the findings *and recommendations* of the National Academy of Sciences") (emphasis added). Yet, in this case, Congress did not require that EPA issue a rule consistent with the "recommendations" proposed in the NAS Report. Rather, it referred to a more general concept: consistency with "the principles" of the NAS Report.

Further, EPA's interpretation avoids a reading of the Appropriations Act that renders some words of the statute redundant. *See Gustafson v. Alloyd Co.*, 513 U.S. 561, 574 (1995) (courts should avoid a reading of statute which renders some words altogether redundant). The Appropriations Act specifically requires that the Research Rule establish a Human Subjects Review Board. SPA1. Yet, Recommendation 6-2 of the NAS Report recommends that EPA establish a Human Studies Review Board. A258. If "principles" means "recommendations," there was no reason for Congress to address expressly the Human Subjects Review Board in the Appropriations Act when it was already included as an NAS Report recommendation. In sum, EPA's interpretation of the statutory language to require consistency with principles proposed by the NAS, rather than the specific recommendations made, is reasonable.

EPA complied with this congressional directive by undertaking a careful reading of the NAS Report and identifying the numerous instances where the NAS Report refers to "principles." 71 Fed. Reg. at 6164 (SPA30). Based upon this review, EPA identified three principles contained in the NAS Report, which corresponded to the three fundamental ethical principles defined by the Belmont Report.[13] *Id.* These three principles are:

> (1) respect for persons – "the [voluntary informed] consent requirement expresses the principle of respect for persons, including respect for and promotion of autonomous choices," A243 (NAS Report);
>
> (2) beneficence – "determining whether the principle of beneficence has been satisfied requires balancing the anticipated risks to study participants against the anticipated benefits of the study to society," A230 (NAS Report), A179; and
>
> (3) justice -- equitable selection of subjects "derives from the principle of justice identified in the Belmont report." A237 (NAS Report).

EPA's interpretation of the Appropriations Act's language of the "principles proposed in" the NAS Report as referring to the three principles of the Belmont Report is reasonable because of the NAS Report's repeated references to these principles, which form the basis for many of the recommendations contained in the NAS Report. Although the NAS Report recognizes and refers to the broad body of documents that have been developed over the years for guiding the evolution of ethical standards for human research, the NAS Report parsed that body of

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[13] The Belmont Report is formally titled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. A1286.

standards and selected the principles of respect of persons, beneficence, and justice as the primary three principles that should inform use of human subjects in research. *See, e.g.*, A221 (" . . . the three basic ethical principles governing the protection of research participants – respect for persons, beneficence and justice . . ."). For example, the NAS Report states

> Several of [the recommendations in Chapter 5] reflect the ethical principles presented in the *Belmont Report*: beneficence, justice, and respect for persons. . . . While the discussion of risk-benefit analysis and scientific validity in the two preceding chapters largely reflected ethical considerations based on the principle of beneficence, this chapter focuses mainly on ethical considerations based on the principles of justice and respect for persons. The principle of justice guided the committee's judgments about the selection and recruitment of participants in research and compensation for research-related injuries, while the principle of respect for persons shaped the committee's recommendations about voluntary informed consent by potential research participants.

A236-37 (NAS Report at 113-14); *see also e.g.,* A133, A237 (principle of justice); A135, A243 (principle of respect for persons); A221-22, A230-31 (principle of beneficence). The Research Rule is wholly consistent with these principles of the NAS Report.

The Research Rule is consistent with the principle of respect for persons. This principle invokes standards for voluntary informed consent. The Research Rule contains lengthy, detailed requirements for informed consent in 40 C.F.R. § 26.1116. In general, this section prohibits an investigator from involving a human as a subject unless the investigator has obtained the legally effective informed consent of the subject or the subject's authorized representative. *Id.* The consent must be obtained under circumstances that allow consideration of whether or not to

participate and that minimize the possibility of coercion. *Id.* The information provided to the subject must be in language understandable to the subject, and cannot include any exculpatory language through which the subject waives any legal rights or provides a release of liability for negligence. *Id.*

In addition, the Research Rule specifies eight basic elements of informed consent that must be provided to each subject. These include an explanation of the research, a description of foreseeable risks or discomforts, a description of any benefits to the subject, a disclosure of appropriate alternative procedures that might be advantageous to the subject, and a statement describing the extent to which confidentiality will be maintained. 40 C.F.R. § 26.1116(a)(1)-(5) (SPA39). In addition, the subject must be provided an explanation as to whether compensation or medical treatments are available, an explanation of whom to contact for answers to questions or in the event of injury, and a statement that participation is voluntary and that refusal to participate will not involve a penalty or loss of benefits to which the subject is otherwise entitled. *Id.* § 26.1116(a)(6)-(8) (SPA39). The subject must be told that he or she may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. *Id.* § 26.1116(a)(8) (SPA39). Finally, the subject must be informed of the identity of the pesticide and the nature of its pesticidal function. *Id.* § 26.1116(e) (SPA39). The Research Rule also requires appropriate documentation of this informed consent. *Id.* § 26.1117 (SPA39). Together, these provisions for informed consent are consistent with the NAS Report's principle of respect for persons.

The Research Rule is also consistent with the NAS Report's principle of beneficence. Beneficence requires ensuring that the anticipated risks to study participants are both minimized and outweighed by the anticipated benefits to the subject or to society. The consistency of the Research Rule with this principle is evidenced by several of its provisions. In order for research covered by the Rule to proceed, an Institutional Review Board must determine that risks to human subjects are minimized by the use of procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk. *Id.* § 26.1111(a)(1) (SPA 38). The IRB must also determine that risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that reasonably may be expected to result. *Id.*

Finally, the Research Rule is consistent with the NAS Report's principle of justice, which concerns the equitable distribution of the costs and benefits of the research. This principle requires the equitable selection of subjects, which is an express prerequisite for the approval of research by an IRB. *Id.* § 26.1111(a)(3) (SPA38) (IRB must determine that the "[s]election of subjects is equitable.") In making its assessment, the IRB is required to be particularly attentive to the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons or economically or educationally disadvantaged persons and to ensure as a condition of IRB approval that "additional safeguards have been included in the study to protect the rights and welfare of these subjects." *Id.* § 26.1111(b) (SPA38). Thus, the Research Rule is consistent with all three fundamental principles contained in the NAS Report.

Petitioners' argument that the Research Rule must be consistent with the 17 specific recommendations of the NAS Report suffers from a debilitating flaw: the statute did not require consistency with the NAS Report's "recommendations." Petitioners argue that the congressional intent they purport to find is clear and that no further inquiry is needed under *Chevron* step one. Pet. Br. at 45. Yet, Petitioners' own explanation of this statutory language undercuts any such argument. Petitioners state: "the Report's 'recommendations' were its 'proposals,' and the Report's 'scientific and ethical principles' were its 'recommendations.'" Pet. Br. at 44. Yet, rather than demonstrating "Congress' clear purpose," Pet. Br. at 45, this sentence in fact shows the contrary – had Congress intended EPA to follow the NAS Report's specific recommendations, it would and could have said so.

In addition, Petitioners' argument that "principles" are the same as "recommendations" fails to account for the fact that the NAS Report itself distinguishes between the two concepts. For example, the NAS committee stated that it "explored in great depth *principles* of both ethical and scientific validity in order to make *recommendations* about how accepted *principles* should be applied here." A163 (emphasis added). Similarly, in Recommendation 5-3, which addresses economic inducement, the NAS refers to "the principles of justice and respect for persons." A243. Thus, the NAS distinguished between principles and recommendations. EPA reasonably did so as well.

IV. The Research Rule is Consistent with the Principles of the Nuremberg Code.

The Appropriations Act also directed that the Research Rule be consistent with the principles of the Nuremberg Code. The Nuremberg Code contains ten express "principles." Petitioners argue that the Research Rule is not consistent with the first three Nuremberg Code principles: voluntary consent, prohibition on unnecessary research, and accounting for prior animal research. As explained below, the Research Rule is consistent with each of these principles.

The phrase "consistent with" is an ambiguous phrase that requires the court to defer to reasonable agency determinations. *Natural Resources Def. Council v. Daley*, 209 F.3d 747, 754 (D.C. Cir. 2000); *Environmental Def. Fund v. EPA*, 82 F.3d 451, 457 (D.C. Cir. 1996). The phrase "consistent with" is "flexible statutory language" and does not require an exact correspondence but "only congruity or compatibility." *Nuclear Energy Inst.*, 373 F.3d. at 1269 (quoting *Environmental Def. Fund*, 82 F.3d at 457).

As discussed below, Petitioners and Amici demand an exact correspondence with the Nuremberg Code, but such exactness is not required. For example, Amici assert that "[e]ach and every principle of the Nuremberg Code, in short, has to be incorporated in the EPA rule *in full* . . . ." Amici Br. at 25 (emphasis added). If that was what Congress intended, it could easily have specified in the Appropriations Act that the rule shall incorporate in full the principles of the Nuremberg Code. It did not do so, and instead set forth the more flexible yardstick of consistency.

A. The Research Rule is Consistent with the Nuremberg Principle of Voluntary Consent and the Related Provision of FIFRA.

The first principle of the Nuremberg Code provides:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.

A529.

As explained above in the discussion of the principle "respect for persons," the Research Rule contains thorough and detailed provisions ensuring informed consent. *See supra* at 40-41. It requires voluntary consent, without circumstances of coercion or undue influence, and with full disclosures to the subjects of the material information about the study and its potential consequences. *See supra* at 40-41; 40 C.F.R. § 26.1116(a)(1) (SPA39).

Petitioners cite examples of studies with disclosures they identify as misleading, Pet. Br. at 49-50, but these examples demonstrate the need for and the adequacy of the Research Rule. The studies cited by Petitioners all took place *prior* to adoption of the Research Rule, at a time when EPA had no regulations governing intentional dosing studies conducted by third parties. By adopting the Research Rule, the types of misleading statements in the informed consent materials cited by Petitioners would no longer be permitted. Petitioners' example of third-party researchers referring to a pesticide as a "drug," Pet. Br. at 49, is

addressed by the Research Rule's requirements that the subject of research involving intentional exposure to a pesticide be informed of the identity of the pesticide and the nature of its pesticidal function. *See* 40 C.F.R. § 26.1116(e) (SPA39). Amici's example where the researcher did not identify the test substance as a pesticide or describe potential health effects would also be contrary to the Research Rule's requirements. Amicus Br. at 20-21. Other inaccurate statements regarding foreseeable risks or potential benefits would violate the informed consent requirements of the Research Rule. Petitioners' examples thus serve to provide strong evidence of the need for the Research Rule to govern third-party research involving pesticides, rather than supporting Petitioners' apparent argument that the Rule should be vacated in its entirety.

Petitioners nonetheless argue that the Research Rule is inconsistent with this first Nuremberg principle in three ways, but each argument lacks merit. First, Petitioners contend that the Research Rule is inconsistent with the first Nuremberg Code principle because the rule allows consent to be provided by the subject's legally authorized representative. However, allowing consent by authorized representatives does not make the Research Rule inconsistent with the Nuremberg Code. Initially, EPA notes that the operative word in the Nuremberg Code provision related to legal capacity is "should." The principle does not state that the person involved "must" or "shall" have legal capacity to give consent. The use of the word "should" indicates a preferred approach but not an approach required in every circumstance. In circumstances where a person does not have independent

legal capacity to give consent, the Nuremberg Code does not prohibit consent from being provided by a legal representative who has been given the capacity to provide consent.

Second, the concern with consent by legal representatives generally arises when a parent consents to the participation of his or her children as human subjects. However, the Research Rule prohibits EPA from conducting or supporting research involving intentional exposure of children. 40 C.F.R. §§ 26.202, 26.203 (SPA34-35). It further prohibits third parties from conducting or sponsoring research involving intentional exposure of children where the research is intended for submission to EPA under FIFRA or FFDCA. *Id.* Subpart L (SPA40). Thus, the issue of legal representatives providing consent on behalf of children for their participation in research involving intentional exposure is not at issue because of the prohibitions on using children as subjects under the Research Rule.

In the case of other persons who are not able to provide informed consent, the Research Rule follows the well-recognized exception for legal representatives contained in the ethical codes and standards governing human research developed in the 50 years following the publication of the Nuremberg Code. The primary authorities relating to the ethical conduct of research with human subjects – the Common Rule, the Declaration of Helsinki and the Belmont Report – provide that consent may be given by a legal representative in cases where the subject does not have the legal capacity for consent. 40 C.F.R. § 26.116 (Common Rule); A1284

(Declaration of Helsinki); A1293-94 (Belmont Report). The NAS Report also recognizes that consent by legal representatives is appropriate in certain circumstances. A135, A243. Numerous federal agencies and departments, including the EPA, adopted this evolved standard for informed consent in the Common Rule, which governs research conducted or supported by federal agencies, by allowing consent to be provided by legally authorized representatives. *See* 56 Fed. Reg. 28,003; 40 C.F.R. § 26.111(a)(4). Since 1991, the Common Rule has governed human subjects research conducted or supported by EPA, including that relating to pesticides. EPA believes the Common Rule is compatible with the Nuremberg Code and with the congressional requirement in FIFRA that prohibits tests on a human being absent the consent of that person. *See* 7 U.S.C. § 136j(a)(2)(P).

The other two objections raised by Petitioners seek more stringent requirements but, in both cases, the language of the Research Rule is consistent with the Nuremberg Code. Petitioners cite to the Nuremberg Code's requirement that "the person involved should have sufficient knowledge and *comprehension* of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision." Pet. Br. at 53 (emphasis in Pet. Br.).[14]

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[14] In their brief, Petitioners incorrectly assert that the NAS Report determined that the Common Rule standards were so inadequate that subjects often do not understand the research in which they are participating. Pet. Br. at 53. However, when the NAS committee made that statement, it was not specifically talking about the standards in or limitations of the Common Rule; it was speaking about the general comprehension level of subjects who participate in any human studies, not

The Research Rule requires that the "information that is given to the subject or the representative shall be in language understandable to the subject or the representative." 40 C.F.R. § 26.1116 (SPA39). EPA reasonably believes that a person will gain sufficient comprehension if the information given is in language understandable to the subject. The Appropriations Act required that the Research Rule be consistent with the principle that a person have sufficient knowledge and comprehension, and the Research Rule is compatible with this principle.[15/]

Finally, Petitioners claim that the Research Rule is not consistent with the Nuremberg Code requirement that human subjects be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, or overreaching. Pet. Br. At 53-54. The Research Rule provides that the "investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." 40 C.F.R. § 26.1116 (SPA39). Minimizing the possibility of

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just those governed by the Common Rule. *See* A243-44.

[15/] Petitioners' preferred approach is not consistent with a NAS Report recommendation. Recommendation 5-4 suggests that EPA develop and disseminate to relevant IRBs, investigators, and sponsors a list of best practices regarding informed consent. Significantly, the NAS drew a distinction between EPA-sponsored tests and third-party tests in making this recommendation. The NAS recommended that EPA should require the use of best practices in studies it sponsors or conducts but, significantly, for third-party studies it recommended that EPA only "encourage all sponsors and investigators to adopt these practices." A245.

coercion or undue influence does not exactly replicate the Nuremberg language, but exact correspondence of language is not required. The language of the Research Rule is compatible with the principle of the Nuremberg Code.

Petitioners argue that the Research Rule does not adequately protect prisoners. Pet. Br. at 54-55. The Research Rule's provisions are adequate to protect prisoners in the extremely unlikely event that someone proposed to conduct such a study. EPA has never conducted or supported any human studies with prisoner subjects, none has been submitted to EPA for many years, and EPA does not expect any new studies on prisoners. 71 Fed. Reg. at 6153 (SPA19). In the event such a study were to be proposed, it would be subject to the Research Rule's requirements, including those requiring special safeguards for prisoners. 71 Fed. Reg. at 6154 (SPA20); 40 C.F.R. § 26.1111(a)(3); 26.1111(b) (SPA38). EPA has also stated its intent not to approve such a study, absent a compelling justification. 71 Fed. Reg. at 6154 (SPA20). Thus, the Research Rule provides adequate protection for prisoners. *Id.*

In each of these instances of alleged inconsistency, EPA's Research Rule is consistent with the Nuremberg Code. As discussed above, the phrase "consistent with" leaves EPA with some flexibility in crafting standards. *Nuclear Energy Inst.*, 373 F.3d at 1273. EPA has not stretched this flexibility to include terms that are inconsistent with the Nuremberg Code. *Id.* Therefore, the Court should find EPA's informed consent provisions consistent with the first principle of the Nuremberg Code.

B. The Research Rule is Consistent with the Nuremberg Code's Third Principle Because the Anticipated Results Will Justify the Performance of the Experiment.

The Third Nuremberg principle states that

> [t]he experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

A529. The Research Rule is consistent with this standard.

The protocol review process required by the Research Rule provides consistency with this Nuremberg principle. Any person who intends to conduct or sponsor human research involving intentional exposure and intended for submission to EPA under the pesticide laws must first submit detailed information to EPA for review and approval before initiating the research. 40 C.F.R. § 26.1125 (SPA40). This information includes a discussion of potential risks to human subjects, measures proposed to minimize such risks, the nature and magnitude of all expected benefits, alternative means of obtaining information comparable to what would be collected through the proposed research, and the balance of risks and benefits of the proposed research. *Id.* § 26.1125(a) (SPA40). As part of EPA's review, EPA has access to all available laboratory animal studies on the potential toxicity of the pesticide because that information is required to be submitted to EPA under FIFRA Sections 3(c)(1) and 6(a)(2), 7 U.S.C. §§ 136a(c)(1) and 136d(a)(2). EPA considers the animal studies and the materials required to be submitted under the Research Rule prior to approving the study.

In addition, the Human Studies Review Board established by the Research Rule conducts an additional review of proposed studies. After EPA staff conduct an initial evaluation of proposed research, EPA must submit the research protocol and all supporting materials to the HSRB. 40 C.F.R. § 26.1601(d) (SPA41). The HSRB provides an additional review of the proposed experiment, and again considers the animal studies and the materials required to be submitted under the Research Rule.

These two reviews enable EPA to determine whether the proposed experiment was designed and based on the results of animal experimentation and whether the anticipated results justify the performance of the experiment. Therefore, the Research Rule is consistent with the third principle of the Nuremberg Code.

C. The Research Rule is Consistent with the Second Principle of the Nuremberg Code, Which Requires that the Experiment Yield Fruitful Results Not Procurable by Other Methods.

The second principle of the Nuremberg Code provides:

> The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature.

A529. Again, the procedures required by the Research Rule for prior review and approval are consistent with this principle.

The IRB, EPA and HSRB procedures are all consistent with this provision. The Research Rule provides that an IRB shall not approve proposed research unless "[r]isks to subjects are reasonable in relation to anticipated benefits, if any,

to subjects, and the importance of the knowledge that may reasonably be expected to result." 40 C.F.R. § 26.1111(a)(2) (SPA38). As discussed in the prior section, both the EPA and HSRB review processes require consideration of alternative means of obtaining information comparable to what would be collected through proposed research and require balancing the risks and benefits of the proposed research. *See* 40 C.F.R. §§ 26.1125(a), 26.1601(d) (SPA40-41). EPA will approve a proposal for research with human subjects and accept reports of such research *only* if it determines that the research is likely to yield fruitful results for the good of society. *See* A1278. Such a study would not be "random or unnecessary" in nature, particularly following consideration of information provided about alternative means of obtaining the information. Thus, the Research Rule is consistent with the second principle of the Nuremberg Code.

CONCLUSION

For reasons stated above, the petitions for review should be dismissed or denied.[16/]

Respectfully submitted,

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16/ In the event the Court finds any part of the Research Rule unlawful, it should remand the Rule to EPA for further proceedings but should not vacate the Rule. As discussed above, the Research Rule fills a regulatory gap in which third-party intentional dosing human toxicity studies were generally unregulated. In a case like this, where Petitioners favor the steps EPA has already taken, but challenge the Research Rule in order to force EPA to take further steps, remand without vacatur is appropriate. *See Fertilizer Inst. v. EPA*, 935 F.2d 1303, 1312 (D.C. Cir. 1991).

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

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Dated: November 16, 2006

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United States Court of Appeals

for the

Second Circuit

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Petitioners,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondent.

ON PETITION FOR REVIEW OF AN ORDER OF THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BRIEF OF AMICI CURIAE SENATOR BARBARA BOXER, SENATOR BILL NELSON, CONGRESSMAN HENRY A. WAXMAN, and CONGRESSWOMAN HILDA SOLIS IN SUPPORT OF PETITIONERS

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INTEREST OF THE AMICUS CURIAE

Amici Senator Barbara Boxer, Senator Bill Nelson, Congressman Henry A. Waxman, and Congresswoman Hilda Solis urge the United States Court of Appeals for the Second Circuit to rule in favor of petitioners. This case turns on whether the EPA's Human Testing Rule, 71 Fed. Reg. 6138-01 (Feb. 6, 2006), encoded at 40 C.F.R. Parts 9 and 26, is inconsistent with the mandate provided by Congress in the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, § 201, Pub. L. 109-54, 119 Stat. 499. Amici were sponsors, co-sponsors, or supporters of the relevant provisions in the Senate and House of Representatives, and have an interest in ensuring that EPA observes both the letter of the statute and its intent.

ARGUMENT

Congress passed a law requiring EPA to promulgate its human testing rule because of the realization that without government controls, humans could be dosed with pesticides without their consent in an effort to weaken safety standards for those pesticides - or at least their consent in any real, freely given sense. Congress was concerned about the potential for human subjects to be injured through their participation in pesticide studies. Congress was particularly concerned about pregnant women, infants, and

children being induced into participating as human guinea pigs. Not only are these subpopulations potentially more sensitive to the effects of pesticides, but pesticide registrants may have a natural desire to conduct research on these subpopulations given that actual data could result in significantly more lenient regulatory standards.

Because EPA's rule fails to prevent this sort of testing, despite Congress's clear instructions to the contrary, we file this amicus brief in support of petitioners. Because EPA's rule is inconsistent with Congress's statutory guidance and the very purpose of Congress's decision to legislate, it must be vacated and remanded.

I. EPA Failed To Follow Congress's Clear Intent To Prohibit Pesticide Testing On Pregnant Women And Children.

The plain language of the statute establishes that Congress wanted pesticide testing on pregnant women, infants, and children banned. Congress directed EPA to prohibit "the use of pregnant women, infants, or children as subjects." § 201. The conference report indicated that "[c]oncern is particularly acute for pregnant women, fetuses, and children." H. Rep. No. 109-188 (2005). Congress acted because, as co-sponsor Rep. Hilda Solis noted, "[i]ntentional human toxicity testing has a troubling history that includes manipulation and abuse of the most vulnerable members of society." 151 Cong. Rec. H7018, 7021 (daily ed. July 28, 2005).

Accordingly, as Senator Barbara Boxer explained, a comprehensive regulatory scheme was crucial if "one cares about protecting children and families." 151 Cong. Rec. S7552, 7554 (daily ed. June 29, 2005) (statement of Sen. Boxer).

EPA's rule fails to implement the ban required by Congress. Instead, the rule only prohibits the use of data collected from pesticide experimentation on pregnant women, infants, and children for certain purposes. *See* 40 C.F.R. §§ 26.1701, 26.1702, & 26.1706 (2006).

Specifically, Congress did not limit its instructions to EPA to cover actions pursuant to only two of the many statutes that the agency administers. The statute says that "[s]uch rule shall not permit the use of pregnant women, infants or children as subjects." § 201. The EPA regulation, in contrast, only provides that its regulations "appl[y] to EPA's decisions whether to rely on its actions taken under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. § 136 et seq.) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 346a)." Since EPA's regulation fails by its own terms to apply the ban to its other programs for which human testing may be permissible – and EPA might consider such studies pursuant to its regulatory authority under the Safe Drinking Water Act and the Clean Water Act, for example – it is inconsistent with that

instruction. *See Yellow Transp., Inc. v. Michigan*, 537 U.S. 36, 45 (2002) ("If the statute speaks clearly to the precise question at issue, Congress must give effect to the unambiguously expressed intent of Congress.") (internal quotation marks omitted); *see also Chevron U.S.A., Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 842-843 (1984) ("If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.").

Congress did not, in short, limit its statutory instructions to FIFRA and the FDCA. But because EPA interpreted its instructions as limited to those two regulatory programs, its rule violates the plain meaning of Section 201.

Congress legislated comprehensively because EPA itself has an inconsistent record on the protection of pregnant women, infants and children from the harms of human testing. The agency planned a joint federal-industry study to test the effect of chemicals on Florida children from newborn to three years old as part of the Children's Environmental Exposure Research Study (CHEERS). Michael Janofsky, *Nominee Challenged Over Program on Pesticides*, New York Times, Apr. 7, 2005, at A19. In exchange for participation in these tests, EPA planned to offer participating families $970, a free video camera, a T-shirt, and a framed

certificate of appreciation. David DeCamp, *EPA Drops Contested Pesticide Study,* Florida Times, April 9, 2005.

Congress found EPA's conduct deeply troubling. Florida senator Bill Nelson declared that he had had a "bellyful of this kind of stuff to come in on the citizens of the State of Florida, and I want it stopped." 151 Cong. Rec. S7554, 7554 (daily ed. June 29, 2005) (statement of Sen. Nelson). Congressman Sanford Bishop characterized CHEERS as "a trifecta of unethical, immoral, and unscientific research," 151 Cong. Rec. H3651, 3670 (daily ed. May 19, 2005) (statement of Rep. Bishop), and many others agreed.[1] Congress's concerns are, of course, well-grounded in established science, as well as ethics. More than a decade before EPA developed the CHEERS program, the National Academy of Sciences raised concerns that exposure of children to pesticides like that involved in the CHEERS study may cause "acute organophosphate pesticide poisoning." *See* U.S. House of Representatives, Committee on Government Reform—Minority Staff Special Investigations Division and United States Senate, Office of Senator Barbara Boxer, Environmental Staff, *Human Pesticide Experiments*, at 10

[1] *See also* 151 Cong. Rec. H7018, 7021 (July 28, 2005) (statement of Rep. Solis) (noting that "the Solis-Bishop amendment is supported by environmental and diverse religious organizations and among more than 80,000 others who have written to me saying they oppose the CHEERS study and support a moratorium on this type of testing.")

(June 2005), available at http://www.democrats.reform.house.gov/Documents/20050627115401-68567.pdf. (last visited Oct. 2, 2006) (A678[2]) [hereinafter *Human Pesticide Experiments*].

The CHEERS study provided unethical incentives and misleading disclosures and was much more than simply an observational study. Through the study, EPA directly encouraged and endorsed the exposure of very young children to toxic pesticides, placing them in harm's way and changing the status quo.

Congress accordingly tried to make sure that its intention to ban testing on pregnant women, infants, and children was very clear. The floor statements of the sponsors and supporters of the bill reaffirm the intent that EPA's implementation ignores. "A [floor] statement of one of the legislation's sponsors ... deserves to be accorded substantial weight in interpreting the statute." *Federal Energy Administration v. Algonquin SNG, Inc.*, 426 U.S. 548, 564 (1976); *see also American Trucking Ass'n, Inc. v. ICC,* 697 F.2d 1146, 1149 (D.C. Cir. 1983) (Scalia, J.) (relying on floor statements as part of the relevant legislative history of a statute); *Southeast*

[2] Citations to 'A___' are to the Appendix filed by Petitioners with their Opening Brief.

Shipyard Ass'n v. United States, 979 F.2d 1541, 1546 (D.C. Cir. 1992) (relying on floor debate to establish legislative intent).

Senator Bill Nelson observed that "[a]ny exposure of an infant child or a pregnant woman to a toxin basically should be prohibited, even in doses that are not expected to do any harm." 151 Cong. Rec. S7552, 7554 (daily ed. June 29, 2005) (statement of Sen. Nelson). He did so because, as he explained, "[t]he human testing of pesticides offers no therapeutic benefit." *Id.* Congressman Alcee Hastings noted that the legislation Congress passed "stops EPA from intentionally exposing pregnant women and children to pesticides." 151 Cong. Rec. H6941, 6942 (daily ed. July 28, 2005) (statement of Rep. Hastings).

EPA's failure to follow Congress's clear instructions, given in both the language of the statute and floor debates, prohibiting pesticide testing on pregnant women, infants, and children is sufficient reason to vacate and remand the rule to the agency.

II. Congress Intended Consistency Between the Rule and the Seventeen Principles Set Forth in the 2004 National Academy of Sciences Report, Not the More General "Belmont Principles."

Section 201 was Congress's attempt to set minimum ethical and scientific requirements for EPA's human testing rule. Congress recognized that in absence of guidelines, EPA had been reviewing "over 20 human

dosing studies . . . [that] routinely violate ethical and scientific standards laid out in the Nuremburg Code, the Declaration of Helsinki, the 'Common Rule,' and the National Academy of Sciences recommendations on human testing." *See* 151 Cong. Rec. S7553 (daily ed. June 29, 2005) (statement of Sen. Boxer) (describing statements made prior to Conference supporting two competing amendments considered by the Senate, one also applying to "third-party intentional human dosing studies for pesticides"). Accordingly, Congress sought to constrain the EPA's discretion by putting something "in place that would guide these experiments" and EPA's use and consideration of them. *See id.*

Congress incorporated the principles of the 2004 NAS report into the protections it wanted EPA to provide test subjects. In fact, it said in Section 201 that the EPA rule "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences." The only exceptions to strict compliance with that report would be for occasions where the express language of section 201 provided for other, independent protections, such as the ban on the use of pregnant women, infants, and children as test subjects. This report contained seventeen concrete "recommendations to strengthen oversight and provide guidance for the use of intentional human dosing studies," A129, which were developed in response to similar concerns as

those before us now, A125-27. These recommendations ranged from issuing guidelines for determining whether intentional human dosing is scientifically valid, A130, to developing best practices for informed consent, A135-36. Moreover, these recommendations were purposefully specific, not general. *See* A129 ("Because of the complexity of the issues considered by the committee and the need to be specific about the proposals being made, the recommendations follow.").

But the EPA failed to comply with the legislative mandate to follow the seventeen recommendations of the 2004 NAS Report. Instead, the EPA relied on "'fundamental ethical principles' identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in its report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the 'Belmont Report')." 71 Fed. Reg. 6138, 6164. In other words, according to the EPA, "principles proposed in the 2004 report of the National Academy of Sciences" refers not to the 2004 NAS Report itself, but to a report mentioned only 12 times within the 208 pages of the 2004 NAS Report. *See* A108-331, *available at* http://darwin.nap.edu/ books/0309091721/html/ (2004) (using search term "Belmont"). Such a conclusion contravenes the plain language of Congress, which nowhere mentioned the report EPA used,

and is unsupported by either traditional statutory analysis or the legislative history. *Chevron U.S.A., Inc.*, 467 U.S. at 842-43 (examining "whether Congress has directly spoken to the precise question at issue" to determine whether to uphold an agency's interpretation of a statute); *see also id.* at 843 n.9 (applying traditional tools of statutory construction). Indeed, aside from conflicting with Congress's clear intent, EPA's sole reliance on the Belmont Report is beyond the scope permitted by Congress. *See id.* at 843-44 (allowing a rule to stand only if it is based on a permissible construction of the authorizing statute). Accordingly, this Court should set aside the human testing rule.

A. Traditional Principles Of Statutory Interpretation Demonstrate That Congress Intended Consistency With The Seventeen Recommendations 2004 NAS Report.

In requiring EPA to rely upon the "principles proposed in the 2004 report of the National Academy of Sciences," § 201, Congress intended EPA to base its rule on the seventeen enumerated scientific and ethical recommendations of the NAS Report. It had no intention of allowing the vague language of the Belmont Report to supersede the seventeen concrete recommendations of the NAS Report. While the Belmont Report is referenced in the 2004 NAS Report, neither the Belmont Report nor any principles contained in it are "proposed" in the NAS Report in the sense that

the NAS offered them as "suggestions" or "offerings." *Random House Unabridged Dictionary* 1551 (2d ed. 1993) (defining "propose" as "to offer or suggest (a matter, subject, case, etc.) for consideration, acceptance, or action"). Instead, any principles contained in the Belmont Report were proposed in 1979 by the National Commission. A1286-87; A172-73 (identifying as "basic ethical principles" the concepts of "respect for persons," "beneficence," and "justice" as being put forth by the National Commission).

Indeed, the NAS recognized that it was not "proposing" any of the principles contained in the Belmont Report, in contrast to its seventeen "proposals," which did reflect its "own judgments." A235. The NAS consistently describes the Belmont Report as containing a separate set of principles apart from NAS's own,[3] even though the NAS recognized that the NAS Report may "draw[] on," A234, both the Belmont Report and other

[3] EPA's attempt to characterize the NAS as "mak[ing] the point clearly that they did not propose new principles," 71 Fed. Reg. 6138, 6164, is misleading. Although the NAS did acknowledge that it "was not required to invent the basic *standards* that govern human research in the United States," A127, 156 (emphasis added), the NAS Report focused on determining "how those standards should be applied in the particular case of intentional human dosing studies conducted by third parties for EPA regulatory purposes." A128. In doing so, the NAS recognized "the need to be specific," and thus set forth a series of seventeen new "recommendations to strengthen oversight and provide guidance for the use of intentional human dosing studies at EPA." A129.

"authoritative statements of principle," A127. For example, the NAS Report describes the Belmont Report as the creation of the National Commission. *See* A172 ("The National Commission is perhaps best known for its Belmont Report"). Similarly, the NAS treats the principles of "respect for persons, beneficence and justice" as not its *own* principles, but those contained in the Belmont Report. *See, e.g.*, A173 ("The Belmont Report recommended that additional attention be given to the equitable selection of participants.").

Bare reliance on "respect for persons," "beneficence," and "justice"—without the recommended specificity provided by the NAS Report—must also be rejected as inconsistent with Congress's mandate. Congress stated that the EPA's rule should be "consistent with the principles proposed" in the 2004 NAS Report. § 201. The 2004 NAS Report, in turn, rejected complete reliance on earlier sources of principles, such as the Belmont Report, because they were "frequently unclear, indeterminate, inconsistent, and even contradictory" in terms of providing sufficient guidance to EPA. A235. Thus the NAS proposed its own set of recommendations—recommendations that covered both "scientific and ethical principles"—and even recommended a procedural framework for their implementation. A168. These recommendations are what Congress meant EPA to rely upon, not the "general prescriptive judgments" in the Belmont Report.

Moreover, the "general prescriptive judgments" of the Belmont Report, A1288, cannot reasonably be conflated with the seventeen concrete recommendations—such as developing and disseminating to Institutional Review Boards, investigators, and sponsors a list of best practices for informed consent, A245, and operating on the "strong presumption that data obtained *after* implementation of the new rules that do not meet the ethical standards described in this report will not be considered," A250 (emphasis in original)—of the NAS Report. *See Sierra Club v. EPA*, 356 F.3d 296, 306 (D.C. Cir. 2004) (recognizing that an agency cannot take an action that abandoned or supplanted the model upon which Congress mandated the action be "based"). The Belmont Report provides "ethical" principles, rather than the scientific and ethical principles of the NAS Report. A1288-89.

This plain-language interpretation of Congress's mandate as requiring EPA to rely upon the seventeen recommendations in the NAS Report is further supported by the interpretive canon of deriving the meaning of a word "from the company it keeps." *Gustafson v. Alloyd Co.*, 513 U.S. 561, 575 (1995). Here, Congress specifically listed two sets of "principles" with which EPA's rule must be consistent: the 2004 NAS Report, and the "Nuremberg Code with respect to human experimentation." § 201. The

Nuremburg Code, much like the 2004 NAS Report, contains ten standards providing specific directives to guide human experiments: from emphasizing the absolute essentiality of voluntary consent," A529, to allowing the conduct of human experiments only if the studies provide results "unprocurable by other methods or means of study," *id.*, to avoiding "all unnecessary physical and mental suffering and injury." *Id.* The structural similarity of the ten principles of the Nuremberg Code with the seventeen principles in the 2004 NAS Report (and the structural dissimilarity of the principles in the Nuremburg Code with the three general concepts of the Belmont Report) further establishes Congress's intent that EPA rely on the actual principles set forth by the NAS Report, not the NAS's report minimal reference to the Belmont Report. Otherwise, "principles" would be ascribed a meaning "so broad that it is inconsistent with its accompanying words, thus giving 'unintended breadth to the Acts of Congress.'" *Gustafson*, 513 U.S. at 575 (citing *Jarecki v. G.D. Searle & Co.*, 367 U.S. 303, 307 (1961)).

B. The Legislative History Also Supports The Use Of The Seventeen Recommendations In The 2004 NAS Report.

The legislative history behind the Congressional mandate further establishes its intent that EPA rely on the seventeen standards set forth by the NAS in its 2004 Report, rather those described by the National Committee in its Belmont Report. *See Chevron*, 467 U.S. at 843 n.9 (urging

reliance on "traditional tools of statutory interpretation," including legislative history); *see Babbitt v. Sweet Home Chapter of Cmty for a Great Or*, 515 U.S. 687, 704-08 (1995) (examining Senate and House Reports to hold that Congress intended the challenged "take" provision "to apply broadly to cover indirect as well as purposeful actions"). The discussions in the House debate regarding the Conference Report to which Section 201 was attached on July 28, 2005, not only consistently refer to the 2004 NAS Report and fail to refer to the Belmont Report, but also require compliance with "stringent criteria," which is lacking in the Belmont Report. 151 Cong. Rec. H7019 (daily ed. July 28, 2005).

As Representative Norman Dicks stated in his introduction to the Conference Report, both the House and the Senate, in the conference report, wanted EPA to stop the use of humans during pesticide testing "until EPA develops regulations reflecting the recommendation of the National Academy of Science [sic] and follows the Nuremburg protocols." 151 Cong. Rec. at H7019; *see also* 151 Cong. Rec. at H7021 (Rep. Solis) (criticizing EPA's earlier proposed rule as "contrary to the recommendations of the NAS and the ethical guidelines of the Nuremburg Code that we require in this amendment"). This language tracks the language used in the 2004 NAS Report for its seventeen principles—that is, "recommendations,"

A129. This language also demonstrates that Congress wanted EPA to follow those proposals actually put forth by the NAS, rather than simply those that might have been referred to by the NAS in its 2004 Report.

III. The EPA Rule Is Inconsistent With The Nuremberg Code That Congress Adopted By Statute.

Congress required EPA to act consistently with the Nuremberg Code because that code reflects the importance of obtaining meaningful consent before any tests can be conducted on humans for non-therapeutic purposes. The Nuremberg Code was devised by American and foreign prosecutors in the aftermath of World War II in the face of the terrible extremes to which human experimentation had been taken in Germany at that time. It is a document grounded in fundamental principles of human rights, adopted by countries around the world and agencies within the United States as the appropriate basis for the responsible and respectful use of human subjects for the purposes of scientific experimentation.

And Congress has made it the law for EPA to follow in this case. Congress required EPA to promulgate "strict scientific and ethical requirements that are consistent with . . . the principles of the Nuremberg Code," to ensure scientific rigor and to prevent ethical abuses in intentional human dosing toxicity studies for pesticides. *See* § 201.

EPA failed to follow Congress's instruction. The first principle articulated in the Nuremberg Code states:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. . . .

A529.

The EPA's rule does not conform to the Nuremberg principle of voluntary consent because the EPA rule violates the standards of 1) individualized personal consent 2) informed consent and 3) voluntary consent.

Nor is this new. Senator Boxer noted that studies had in the past "routinely violate[d] ethical and scientific standards laid out in the Nuremberg Code." 151 Cong. Rec. at S7553 (statement of Sen. Boxer).

These violations prompted Congressional action. Congress' goal was to stop EPA from relying on studies that lacked fundamentally fair consent. As Representative Solis explained, Section 201 was designed to ensure that "EPA may not consider or rely on any intentional human-dosing study that does not meet the minimum ethical and scientific criteria recommended by

the Nuremberg Code."[4] 151 Cong. Rec. H7021, 7021 (daily ed. July 28, 2005) (statement of Rep. Solis).

Under the EPA rule, any "legally authorized representative" may give consent. 40 C.F.R. §§ 26.1116, 26.1117(a), (b)(1) & (b)(2). As defined by the EPA, a "legally authorized representative" is an "individual or judicial or other body authorized under applicable law to consent on the behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." 40 C.F.R. § 26.1102(c). By defining "legally authorized representative" under "applicable law," the meaning of "consent" varies depending on the site of experimentation – including sites in foreign countries that have not accepted American concepts of individual rights or the necessity of individual consent. Congress did not provide for consent by a representative and the Nuremberg Code expressly requires "[t]he voluntary consent of the human subject." EPA's rule violates the standard of

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[4] As we observed in Part I of this brief, *supra*, sponsor statements "greatly aid in making the [statute's] purpose apparent." Max Radin, *A Short Way With Statutes*, 56 Harv. L. Rev. 388, 411 (1942); *see also Pub. Employees Ret. Sys. v. Betts,* 492 U.S. 158, 179 (1989) (giving weight to Senator Yarborough's views on the construction of the Age Discrimination in Employment Act because he was a sponsor); *Pacific Gas & Elec. Co. v. Energy Res. Conservation & Dev. Comm'n*, 461 U.S. 190, 220 n.23 (1983) (relying on a 1965 explanation by "an important figure in the drafting of the 1954 [Atomic Energy] Act"); *see, e.g., National Endowment for the Arts v. Finley,* 524 U.S. 569, 573-74 (1998) (sponsors' statements); *Conroy v. Aniskoff,* 507 U.S. 511, 516-17 & n. 12 (1993) (sponsors' statements).

individualized consent because it expressly allows "consent" to be given by an entity other than the human subject.

EPA's rule also fails to ensure that the human subject is appropriately informed of the risks presented by the research. The Nuremberg Code similarly explains, "before the acceptance of an affirmative decision by the experimental subject there should be made known to him … all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment." Contrarily, the EPA rule adopts old practices that have led to widespread misunderstanding about research risks among the subjects of that research. *See Human Pesticide Experiments* at 35-38 (finding that prior pesticide experiments on humans used such complex language in their consent forms that it is unlikely the volunteers understood the risks) (A703-05). The EPA's rule disseminates a pre-existing standard that has led to common violations of the Nuremberg Code's informed consent requirements.

EPA's rule similarly fails to ensure that human subjects who provide consent do so voluntarily. The Nuremberg Code demands that the human subject be "so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching,

or other ulterior form of constraint or coercion." Instead of adopting the Nuremberg's clear and absolute standard, EPA's rule provides for human studies to include undefined "additional safeguards" to protect "the rights and welfare" of subjects who "are likely to be vulnerable to coercion or undue influence." 40 C.F.R. § 26.1111. The indefinite standards allow total discretion to the conductors of the experiment.

There are significant deficiencies in the informed consent of the subjects tested in several of the experiments on which EPA has in the past relied, including the inadequate disclosure of potential harms, complex language, easily misunderstood consent forms, and plainly not obtaining consent.

Some experiments featured consent forms and accompanying information sheets that failed to explain or downplayed the health risks associated with the pesticide exposures involved in the experiments. *See Human Pesticide Experiments* at 35-38 (stating that the potential harms were not adequately disclosed Chloropicrin, Dimethoate, Amitraz (1998) and Amitraz (1992) studies) (A 703-05).

For example, consent forms in experiments involving dimethoate did not explain the relevant risks. The Dimethoate Experiment (2004), an organophosphate pesticide manufactured by BASF, utilized a consent form

that does not identify the test substance as a pesticide or describe potential health effects. *Human Pesticide Experiments* at 18 (A 686). Dimethoate had been identified by EPA as a suspected carcinogen, a developmental toxicant, and a neurotoxicant. Scorecard: the Pollution Information Site, *Chemical Profile: Dimethoate,* http://www.scorecard.org/chemical-profiles/summary.tcl?edf_substance_id=60%2d51%2d5 (last visited Sept. 30, 2006). It is a suspected cardiovascular or blood toxicant, gastrointestinal or liver toxicant, kidney toxicant, and skin or sense organ toxicant. *Id.* The informed consent form used in the Dimethoate experiment did not identify any of these potential risks. *Human Pesticide Experiments* at 18 *(citing* W.J.A. Meuling and L. Roza, *Urinary Excretion Profile of Dimethoate and its Metabolites after Single Oral Administration of Dimethoate in Male Volunteers* (Dec. 28, 2004)) (A 686). Furthermore, the written information presented to test subjects states that "not a single health effect is expected" and characterizes the chemical as "used to protect or cure all kinds of plants, fruits and crops from disease." *Id.*

Even when risks are explained in the consent forms, the language is often so complex that participants do not understand the risks. *See Human Pesticide Experiments* at 35-38 (observing that three prior experiments used such complex language in their consent forms that it was unlikely the

volunteers understood to the risks) (A703-05). In a 1999 Phosmet study, an ethics committee identified "volunteer information [that] is difficult to understand," and recommended that "[s]ome effort should be made to simplify the volunteer information," although researchers declined to make any of these changes. *Id.* at 30 (quoting S. Freestone, S.J. Mair, & P. McFarlane, *A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (June 4, 1999)) (A698).

Other studies have not even been able to establish that they ever obtained any kind of consent at all. A 1969 Dichlorvos experiment made no assertion of having obtained any informed consent, and congressional investigators were unable to obtain any evidence of consent from the principals behind 1997 Dichlorvos, 1996 Methyl Isothiocyanate, 1977 Ethephen, 1972 Ethrel, and 1971 Carbamates experiments. *Human Pesticide Experiments* at 35-38 (A703-05).

And of course, some terribly tragic cases of uninformed consent are not unknown to the federal government.[5] Nor are they unknown elsewhere.

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[5] Consider the uninformed consent provided by the victims of the Tuskegee Syphilis Study, 400 of whom were permitted to suffer from the disease although the United States Public Health Service had a cure readily available for them. Experimenters continued this study even though a proven and 100% effective cure for syphilis had already been found. Barbara A. Noah,

EPA has documented troubling examples of English test subjects being dosed with the pesticide "Doom"[6] and Scottish subjects with orange juice laced with the insecticide Aldicarb.[7]

This rather sordid history of pesticide testing is particularly troubling because the Nuremberg Code has a long and distinguished history of

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The Participation of Underrepresented Minorities in Clinical Research, 29 Am. J. L. and Med. 221, 230 (2003) (describing how the Tuskegee studies continued some two decades after a cure for syphilis had become available). In some cases, researchers intervened to prevent treatment when other physicians diagnosed subjects as having syphilis. Predictably, many subjects died of syphilis during the study. *See generally Tuskegee's Truths: Rethinking the Tuskegee Syphilis Study* (Susan M Reverby ed. 2000); Robert M. White, *Unraveling the Tuskegee Study of Untreated Syphilis,* 160 Archives of Internal Med. 585 (2000); Department of Health and Human Services: Center of Disease Control and Prevention, *The Tuskegee Timeline,* http://www.cdc.gov/nchstp/od/tuskegee/time.htm (last visited Sept. 28, 2006).

[6] *See* Molly Evans, *The English Patients: Human Experiments and Pesticide Policy*, The Environmental Working Group, July 1998, http://www.epa.gov/oscpmont/sap/meetings/1998/december/english.pdf (last visited Oct. 7, 2006) ("In three related studies conducted just last year for Amvac Chemical Corporation, headquartered in City of Commerce, California, for example, researchers at the Medeval Laboratories in Manchester, England dissolved a neurotoxic insecticide, dichlorvos, in corn oil and paid a small number of adult men to eat it in a test of the chemical's acute effects."). Dichlorvos is often marketed under the name "Doom." *Id.*

[7] *See id.* (documenting study commissioned by Rhone-Poulenc and conducted in 1992 on 38 men and 9 women at the Inveresk Clinical Laboratory in Scotland, "subjects were given a light breakfast on the day of the study, including a drink of orange juice" containing a placebo or various doses of aldicarb, an extremely toxic insecticide resulting in subject reports of "profuse sweating," "headaches," and "light-headedness").

protecting human subjects, as courts, agencies, and the international community have recognized.

The former have recognized that the code "is absolutely essential...to satisfy moral, ethical and legal concepts." *Washington v. Harper*, 494 U.S. 210, 238 (1990) (Steven, J., dissenting). The United States Military Tribunal that established the Nuremberg Code set a standard against which to judge German scientists who experimented with human subjects during the Holocaust. *See United States v. Stanley*, 483 U.S. 669, 687 (1987) (noting that the Nuremberg Code was created as uniform standard to govern scientists of permissible medical experiments in the Nuremberg Trials).[8] The code stands for the principle that "experimentation with unknowing

[8] The Nuremberg Code is the "most complete and authoritative statement of the law of informed consent to human experimentation." *Grimes v. Kennedy Krieger Institute, Inc.*, 782 A.2d 807,835 (Md. 2001); *see also Whitlock v. Duke University* 637 F.Supp. 1463, 1470 (M.D.N.C.1986) (Nuremberg Code was adopted "as a proper statement of the law of informed consent in connection with the trials of German Scientists for human experimentation after World War II"); *Kaimowitz v. Michigan Dep't Mental Health*, No. 73 Civ. 19434-AW (Mich. Cir. Ct., Wayne County, July 10, 1973) (unreported), reprinted in A. Brooks, *Law, Psychiatry And The Mental Health System* 902 (1974) ("In the Nuremberg Judgment, the elements of what must guide us in decision are found. The involuntarily detained mental patient must have legal capacity to give consent. He must be so situated as to be able to exercise free power of choice without any element of force, fraud, deceit, duress, overreaching, or other ulterior form of restraint or coercion. He must have sufficient knowledge and comprehension of the subject matter to enable him to make an understanding decision. The decision must be a totally voluntary one on his part.").

human subjects is morally and legally unacceptable." *Id.* It "requires that the informed, voluntary, competent, and understanding consent of the research subject be obtained." *Grimes v. Kennedy Krieger Inst , Inc.*, 782 A.2d 807,835 (Md. 2001).

But EPA's rule fails to adhere to the code. Although, for example, the Code requires free choice by testing subjects "without the intervention of any element" of, among other things, "over-reaching, or other ulterior forms of constraint or coercion," A529, EPA's rule only requires that coercion be "minimized." The Nuremberg Code, and Congress's statute, is much more comprehensive.

Each and every principle of the Nuremberg Code, in short, has to be incorporated in the EPA rule in full, and the agency has failed to do so in the rule it has promulgated.

CONCLUSION

For the foregoing reasons amici members of Congress urge the court to vacate and remand the Human Testing Rule, 71 Fed. Reg. 6138-01 (Feb. 6, 2006), encoded at 40 C.F.R. Parts 9 and 26, to the agency for reconsideration.

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October 11, 2006

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This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 5,581 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office Word 2003 in a 14 point, Times New Roman font.

October 11, 2006

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Stanley N. Alpert

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